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STUDIES IN THE ANAEMIAS OF INFANCY AND EARLY CHILDHOOD*

PART XIII.—EXPERIMENTS ON BLOOD REGENERATION AND THEIR SIGNIFICANCE FOR THE LIFE SPAN OF ERYTHROCYTES

BY

H. S. BAAR

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham)

The problem of the length of time for which the red cell normally survives in the circulation has been investigated for many years by a great variety of methods and the literature on this subject is enormous. Much of it has been reviewed by Robscheit-Robbins (1929), Isaacs (1937), Schiodt (1938b) and by Dekkers (1939). Study of these reviews reveals a remarkable diversity of estimates, the time allotted by different authors varying from ten to two hundred days in one species of experimental animal and a life span of as much as a year having been suggested by one observer in the case of the erythrocyte in man. The results of many investigations involve the acceptance of a purely hypothetical mechanism for the formation and destruction of red cells ; here will be discussed only those which have a direct relation with the present investigation.

Hunter (1884–86) noticed that the time required for the blood to return to normal after bleeding is almost exactly the same as that required for the removal of excess blood corpuscles in artificial plethora. 'This similarity in the results is probably more than a mere coincidence, and can only be explained by assuming that after loss of blood the return to the normal is effected partly by increased formation, but mainly through a diminished destruction of blood corpuscles; and the time taken for complete restoration probably thus represents approximately the average duration of life of newly-formed red corpuscles.' Boycott and Douglas (1910) were the first to approach the problem by making a thorough investigation of the rate of blood regeneration and their experiments are of particular interest for the total haemoglobin was estimated by the CO-method in their animals. They found that rabbits bled to about two-fifths of their total haemoglobin regenerate their loss at a regular rate of about 0·3 c.c. oxygen capacity per day. 'If P = the normal daily production to make good D, the normal daily loss, and p = the excess production in response to the haemorrhage then P + p − 3/5 D = 0·3 c.c.; assuming that P is still equal to D, 2/5 P + p = 0·3 c.c., from which we can get a definite outside limit that P or D cannot be greater than 0·75 c.c. per day.' The assumption made in this calculation, that the destruction after haemorrhage decreases in proportion to the diminution of haemoglobin is not correct, however, as will be shown later. Schiodt (1937), who has published a series of papers dealing with the regeneration of red cells following blood loss from gastric or duodenal ulcer, gives a more precise but at the same time more one-sided idea as to the mechanism of regeneration and the possibility of estimating the life span of red cells by the 'regeneration time.' If, for example, a life span of twenty-five days is assumed for the R.B.C. this means that 'out of five million cells, every day approximately 200,000 are destroyed to be replaced by new-formed cells. If now a patient with a normal count of five million R.B.C. in one day loses half his blood (and has no subsequent bleeding) he will—after correction of volume—have 2·5 millions left. The haemorrhage has taken place without any selection of the blood lost: thus the 2·5 millions left behind represent as well corpuscles formed the day before as those standing upon the threshold of destruction. The 2·5 millions therefore will disappear in the course of twenty-five days, every day 100,000 will be destroyed. But if the normal production of 200,000 still goes on, there will be a surplus of 100,000 corpuscles daily, in twenty-five days 2·5 millions. Thus the normal count of five millions will be reached at this date.'

From this consideration, which implies that a loss of blood is repaired by the organism merely by a reduction of the number of erythrocytes destroyed daily in proportion to the number actually present at the time immediately following the loss of blood and without any change in the blood formation, Schiodt identifies the life span of the red cell with the time required to repair a loss of blood. Schiodt's idea is supported by the close relation which he and Gram (1936) found between the lowest red cell count and the daily rise in red cells and by the course of recovery. In Schiodt's observations the rise of the erythrocyte count from the lowest point was a straight line and a constant level was reached (in cases treated with Meulengracht's diet) after thirty-three days. If the daily rise in R.B.C. was plotted against the lowest count a practically straight line was obtained 'the equation of which may be expressed as daily rise (in millions) × 33 = 4·54 — lowest count of R.B.C. (in millions).'

* Part XII appeared in the March 1943 issue: Part XIV will appear in the September issue. References will be given at end of Part XIV.

There are, however, a number of observations in the literature which are hard to bring into accord with Schiødt's simple conception and Schiødt himself in a later paper (1938b) was less decided on the mechanism of blood regeneration. Thus the time of repair is not independent of the amount of blood lost. Hühnerfauth (1879) and Lyon (1881) found that in dogs a blood loss of 4·42–4·5 per cent. of the body weight was repaired in thirty-one to thirty-four days, a loss of 3·58–4·27 per cent. of body weight in nineteen to twenty-five days, and of 1·14–2·86 per cent. in seven to fourteen days. In man the blood count became normal after small losses of blood in two to five days, after a haemorrhage of medium degree (1–3 per cent. of body weight) in five to fourteen days and after large losses (about 4 per cent. of body weight) in fourteen to thirty days. Boycott and Douglas (1909a) found that by ' repeated bleedings the rate of regeneration may be increased several times over that which is induced by a single bleeding though the percentage of total oxygen capacity may have been reduced to a lower level by the single bleeding.' Geiling and Green (1921) observed recovery from a single haemorrhage in rats in seven to ten days but from a double haemorrhage in ten to fourteen days. The increase in the number of R.B.C. does not always follow a straight line. Leichsenring and Höring (1931) found little change between two to three days and one week after repeated bleeding of dogs ; the most rapid increase occurred between one and two weeks and this was followed by a slower rise. Similarly those curves of Ritz (1909) representing recovery from phenylhydrazine anaemia resemble more an S-shaped curve whereas those of haemorrhagic anaemia approach a straight line.

It must be realized that a curve representing the rise of haemoglobin or of R.B.C. does not indicate the real regeneration but is the result of two factors, the formation (or, more exactly, the release from the bone marrow) of R.B.C. and their destruction. It was decided therefore to separate these two factors in experimental anaemia, calculating the real regeneration or the daily haemoglobin intake from the number of reticulocytes and their maturation time determined in vitro, and sometimes in vivo, and estimating the destruction subtracting the observed rise of haemoglobin from the intake determined in this way. Among eighteen experiments only four rabbits and two guinea pigs were followed for a sufficiently long time and these only will be reported here with one animal as a control for each species. Anaemia was produced by subcutaneous injections of phenylhydrazine hydrochloride. Rabbit 15 was followed for 128 days, rabbits 17 and 18 for 126 days, rabbit 20 for 79 days and the two guinea pigs for 77 days. Haemoglobin determinations and reticulocyte counts were made three times a week, erythrocyte counts irregularly. Haemoglobin determinations were sometimes made with Haldane's haemoglobinometer, sometimes with Evelyn's photoelectric step-photometer, both standardized by determinations of oxygen capacity with van Slyke's method. In the first week of the experiments only the photometric method was used. At this time the blood of animals poisoned with phenylhydrazine shows a brownish colour which renders visual methods for haemoglobin determinations unreliable. This brown colour was first reported by Domarus (1908) who describes the blood in post-mortem findings as ' chocolate-brown.' It has been studied in greater detail by Price Jones (1911–12). The error in the photoelectric method due to the extinction by the brown pigment in the spectral region of filter 540 is negligible.

The results are recorded in tables 1–6 and in charts I–VI. The charts show the figures for haemoglobin in gm. per cent. and the reticulocyte concentration in 10,000 per c.mm.

It will be seen that the time interval between the lowest and highest haemoglobin level was 12, 13, 19 and 23 days respectively for the four rabbits, 13 and 16 days respectively for the two guinea pigs. The points representing the haemoglobin levels during the recovery from phenylhydrazine anaemia lie on a practically straight line for the rabbits 15 and 17 and for the guinea pigs, whereas in rabbits 18 and 20 a distinct decrease in the speed of recovery will be noticed. For a detailed analysis of the regeneration the following figures are given in tables 1–6 (p. 70). In column 2 the daily regeneration of haemoglobin (= intake) per 100 c.c. blood is noted for the two- or three-day periods indicated in column 1. This figure is calculated by taking the arithmetic mean of two subsequent reticulocyte counts (in per cent.), dividing by 100 and multiplying by 24 over the maturation time in hours. The maturation time was determined during the period of high reticulocyte counts for rabbits both in vitro and in vivo, for guinea pigs in vitro only. These figures, which were 10 hours for rabbits and 8 hours for guinea pigs, were used for the whole experimental period. The regeneration per 100 c.c. blood is therefore given by the formula $\frac{Hb \times R}{100} \times 2{\cdot}4$ for rabbits and $\frac{Hb \times R}{100} \times 3$ for guinea pigs, where Hb is haemoglobin in gm. per cent. and R the reticulocyte count per cent. of red cells. If this figure be multiplied by the blood volume in decilitres the total daily intake of haemoglobin is obtained. Taking the midpoint between two counts not only is the average of a continually changing regeneration approached but errors in haemoglobin determinations and reticulocyte counts are also minimized. In the third column the actual rise or fall of haemoglobin in gm. per 100 c.c. observed in the corresponding period is given. If the drop be added and the rise subtracted from the regeneration figure the destruction of haemoglobin in gm. per 100 c.c. blood is obtained (column 4). The regeneration has been also calculated on the basis of a hypothetical maturation time of twenty-four hours and the figures for destruction thus obtained are given in column 4 in brackets. This calculation gives a new support to the conclusions on the maturation time reached in the previous paper (part XII). It is obvious that the lowest possible limit for haemoglobin destruction is 0, it can never have a negative sign. Column 4

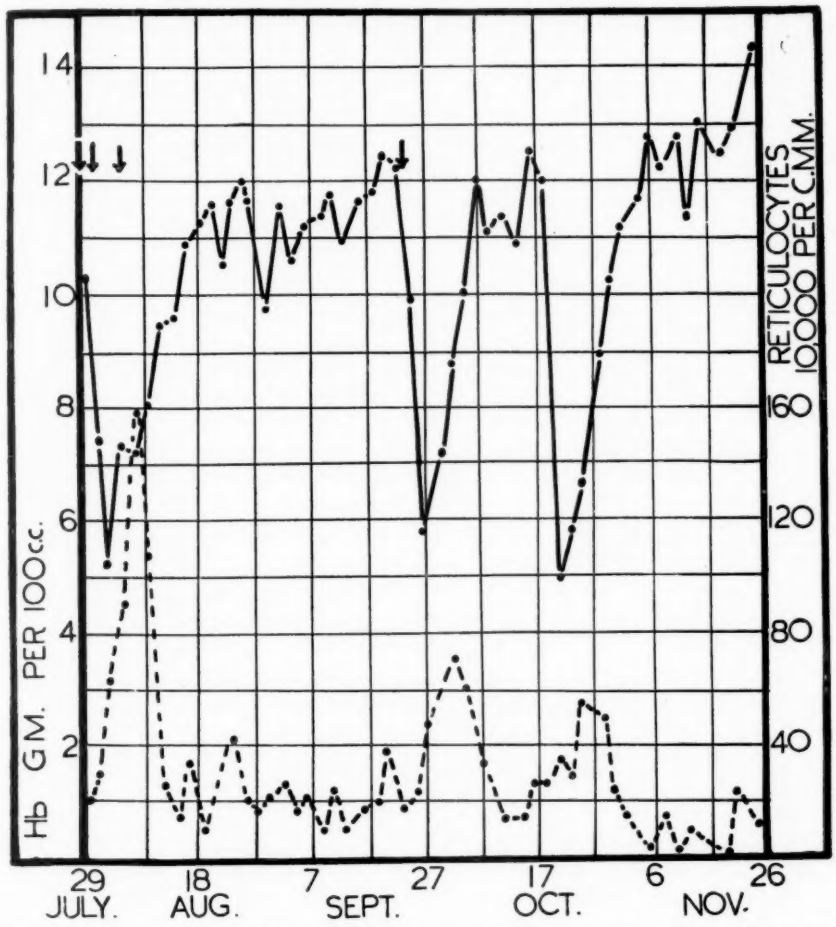

CHART I.—Rabbit No. 15. ——— Haemoglobin in gm. per cent., – – – – reticulocytes in 10,000 per c.mm. Arrows indicate phenylhydrazine injections.

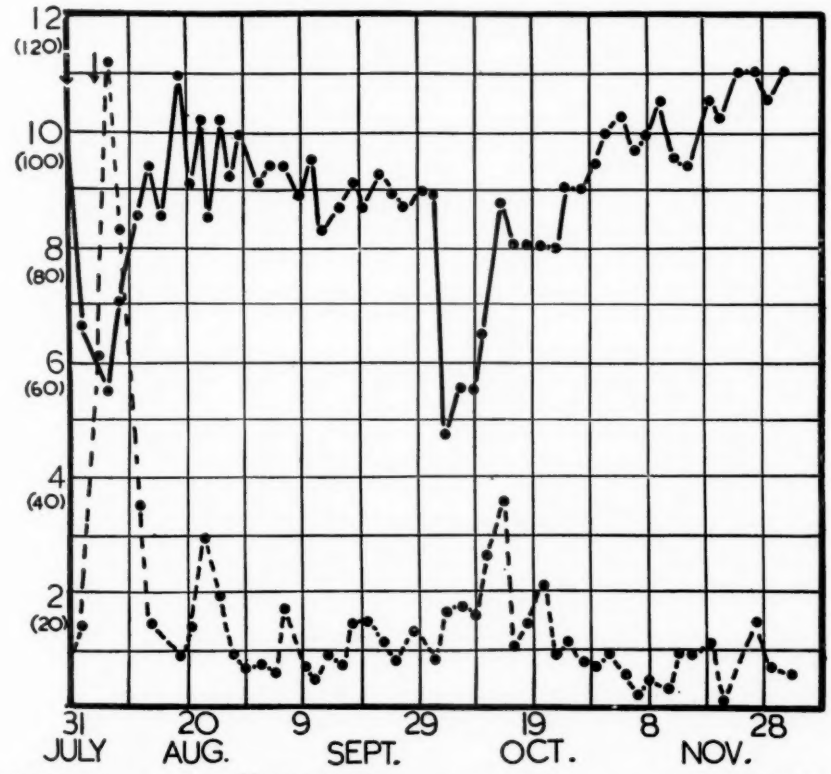

CHART II.—Rabbit No. 17. ——— Haemoglobin in gm. per cent., – – – – reticulocytes in 10,000 per c.mm. Arrows indicate subcutaneous injections of phenylhydrazine hydrochloride.

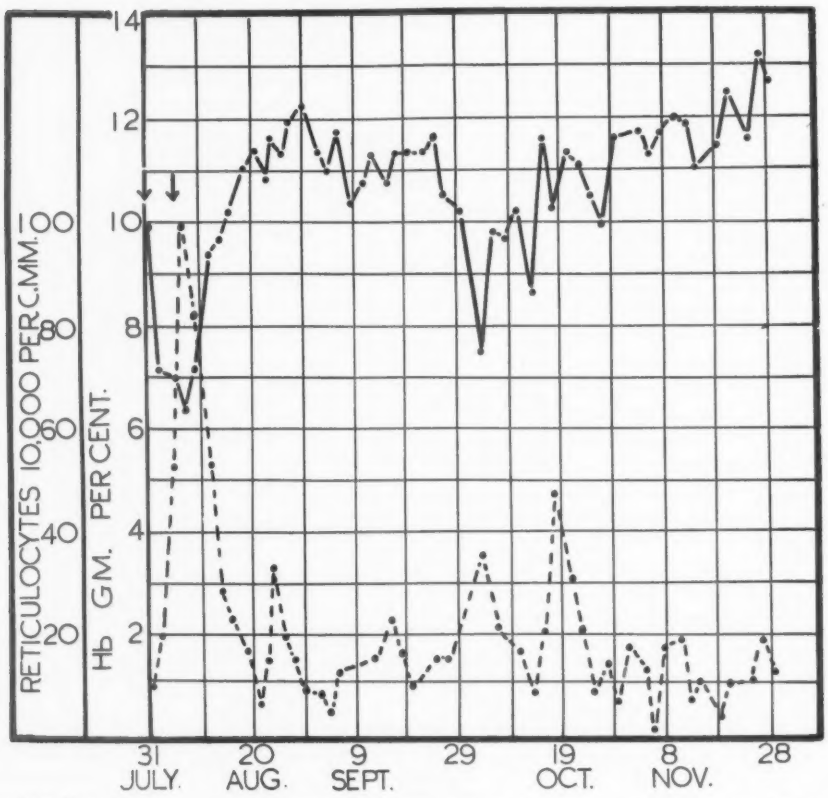

CHART III.—Rabbit No. 18. ——— Haemoglobin gm. per cent., – – – – reticulocytes in 10,000 per c.mm. Arrows indicate injections of phenylhydrazine hydrochloride.

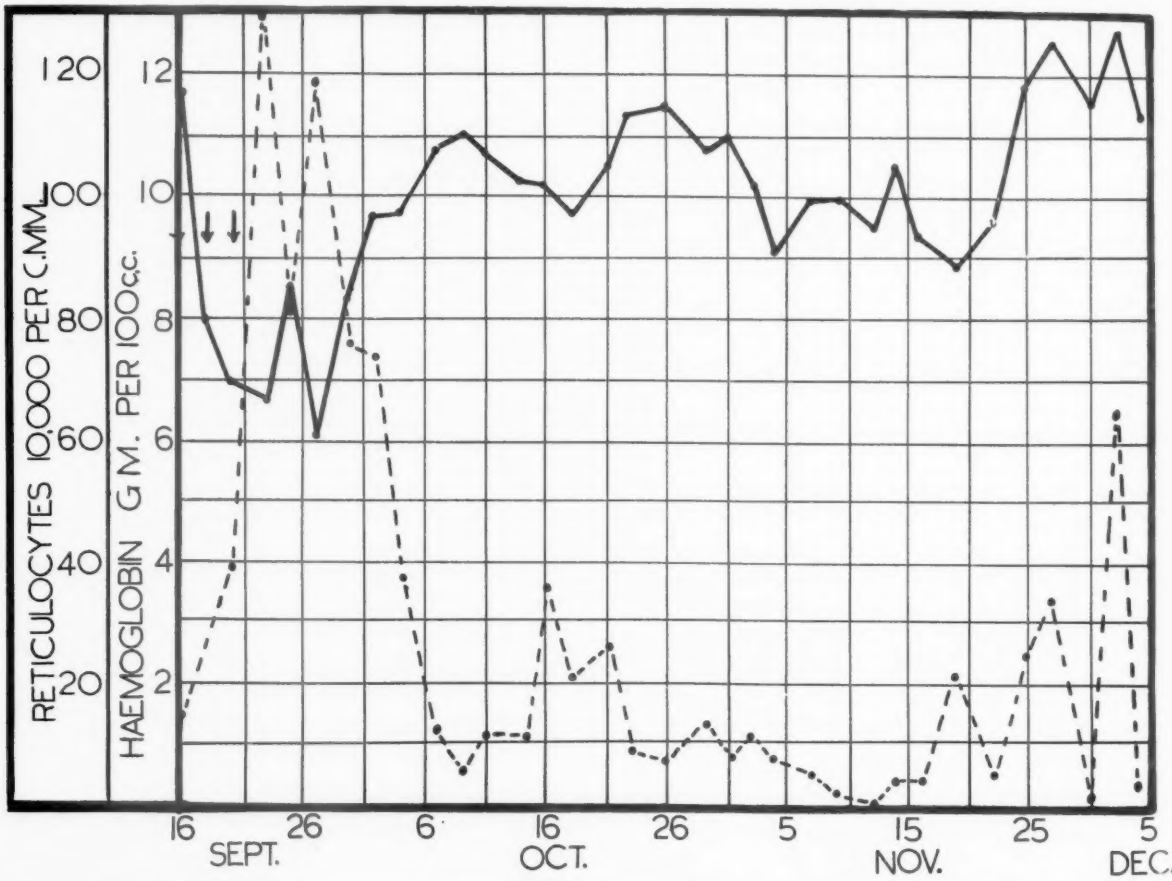

CHART IV.—Rabbit No. 20. ——— Haemoglobin gm. per cent., – – – – reticulocytes in 10,000 per c.mm.

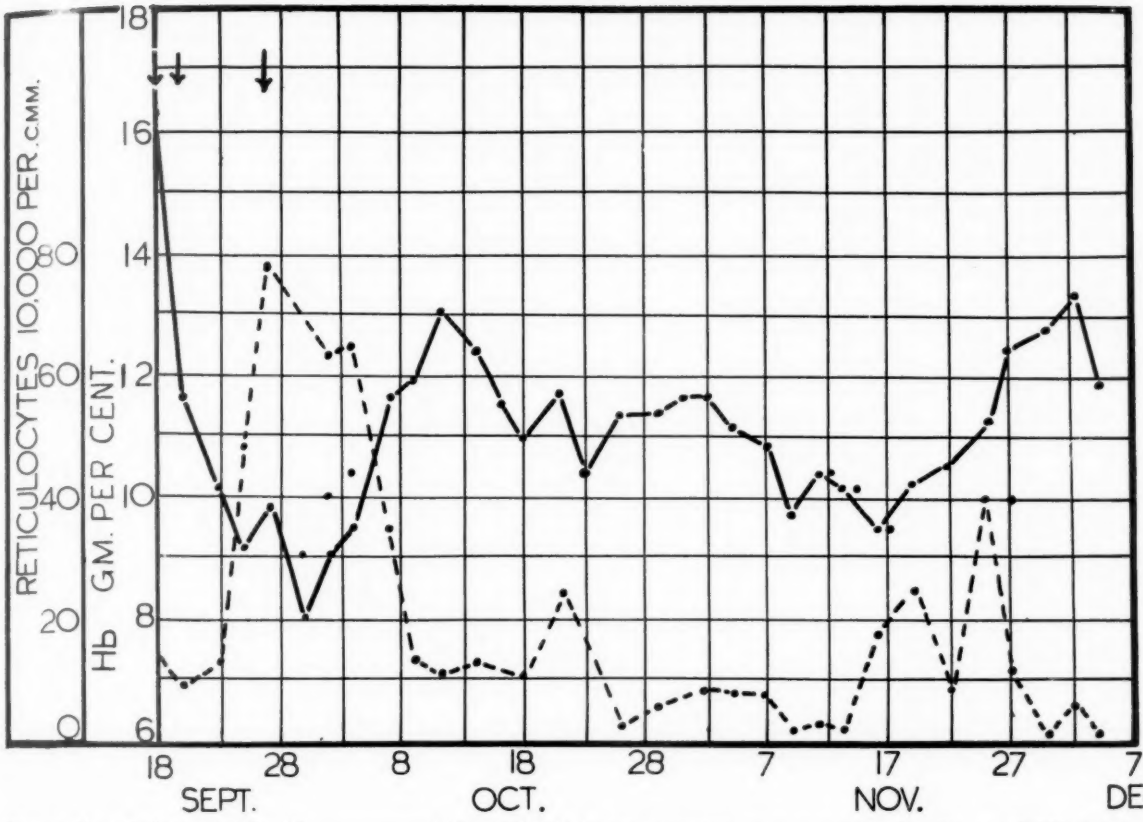

CHART V.—Guinea pig No. 21. ———— Haemoglobin in gm. per cent., – – – – reticulocytes in 10,000 per c.mm. Arrows indicate subcutaneous injections of phenylhydrazine hydrochloride.

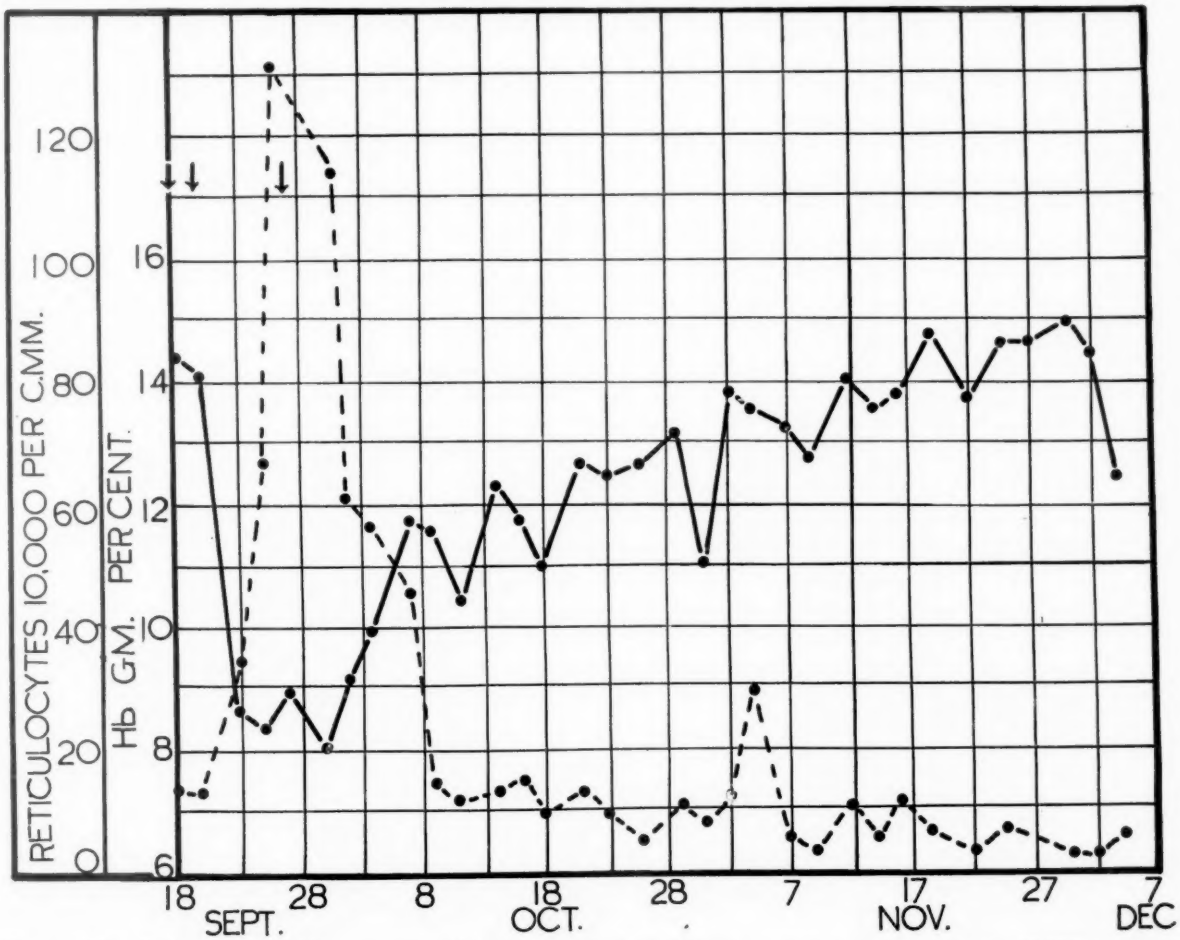

CHART VI.—Guinea pig No. 22. ———— Haemoglobin in gm. per cent., – – – – reticulocytes in 10,000 per c.mm. Arrows indicate subcutaneous injections of phenylhydrazine hydrochloride.

TABLE 1

REGENERATION AND DESTRUCTION OF HAEMOGLOBIN IN PHENYLHYDRAZINE POISONING. RABBIT NO. 15

Date	Regeneration gm. per cent. Hb per day	Gain or loss per day gm. per cent. Hb	Destruction gm. per cent. per day	$\sum\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$
29–31.7.40	1·392	−1·45	2·842 (2·03)	2·784
31.7–2.8.40	2·56	−1·038	3·598 (2·103)	7·89
2–5.8.40	3·90	+0·69	3·21 (0·95)	19·6
5–7.8.4	6·48	−0·069	6·41 (2·769)	32·3
7–9.8.40	6·97	+0·415	6·56 (2.485)	46·2
9–12.8.40	4·42	+0·46	3·96 (1·38)	59·5
12–14.8.40	1·04	+0·069	1·11 (0·364)	61·6
14–16.8.40	1·24	+0·62	0·62 (−0·104!)	64·3
16–19.8.40	1·17	+0·1	1·07 (0·388)	67·8
19–21.8.40	0·83	+0·138	0·69 (0·208)	69·5
21–23.8.40	1·59	−0·415	2·0 (1·078)	
23–24.8.40	2·10	+1·1	1·0 (−0·225 !)	
24–26.8.40	1·68	+0·14	1·54 (0·56)	
26–28.8.40	0·985	−0·14	1·125 (0·376)	
28–30.8.40	1·05	−0·965	2·015 (1·403)	
30.8–2.9.40	1·22	+0·595	0·625 (−0·085 !)	
2–4.9.40	1·12	−0·484	1·604 (0·95)	
4–6.9.40	0·99	+0·28	0·71 (0·095)	
6–9.9.40	0·86	+0·1	0·76 (0·28)	
9–11.9.40	0·93	+0·21	0·72 (0·178)	
11–13.9.40	0·87	−0·83	1·70 (1·192)	
13–16.9.40	0·705	+0·23	0·475 (0·063)	
16–18.9.40	0·98	+0·069	0·91 (0·338)	
18–20.9.40	1·53	+0·35	1·18 (0·288)	
20–23.9.40	1·45	−0·097	1·547 (0·701)	
23–25.9.40	1·17	−1·11	2·28 (1·598)	
25–27.9.40	2·16	−2·06	4·22 (2·96)	
27–30.9.40	2·78	+0·47	2·31 (1·16)	
30.9–2.10.40	3·38	+0·69	2·69 (0·72)	
2–4.10.40	3·44	+0·62	2·82 (0·815)	
4–7.10.40	2·54	+0·65	1·89 (0·405)	
7–9.10.40	1·5	−0·41	1·91 (1·034)	
9–11.10.40	0·97	+0·14	0·83 (0·247)	
11–14.10.40	0·74	−0·18	0·92 (0·488)	2·22
14–16.10.40	1·03	+0·83	0·20 (−0·401!)	4·28
16–18.10.40	1·34	−0·28	1·62 (0·138)	6·96
18–21.10.40	1·96	−2·35	4·31 (3·167)	12·84
21–23.10.40	1·60	+0·41	1·19 (0·255)	16·04
23–25.10.40	2·18	+0·41	1·77 (0·50)	20·40
25–28.10.40	2·80	+0·73	2·07 (0·43)	28·8
28–30.10.40	1·99	+0·69	1·30 (0·137)	32·78
30.10–1.11.40	1·02	+0·41	0·81 (0·015)	34·82
1–4.11.40	0·59	+0·18	0·41 (0·066)	36·59
4–6.11.40	0·63	+0·14	0·49 (0·122)	37·85
6–8.11.40	0·50	−0·225	0·725 (0·433)	
8–11.11.40	0·50	+0·225	0·275 (−0·017)	
11–13.11.40	0·372	−0·70	1·072 (0·855)	
13–15.11.40	0·465	+0·85	−0·385 (−0·656)	
15–19.11.40	0·198	−0·15	0·346 (0·232)	
19–21.11.40	0·61	+0·25	0·36 (0·004)	
21–25.11.40	0·985	+0·38	0·605 (0·03)	
25–27.11.40	0·58	−0·125	0·750 (0·367)	
27–29.11.40	0·314	+0·40	−0·086 (−0·269)	
29.11–2.12.40	0·286	0·0	0·286 (0·119)	
2–4.12.40	0·59	−1·25	1·84 (1·496)	

Injections of phenylhydrazine hydrochloride: 29.7.40 −0·02 gm., 31.7.40 −0·02 gm., 24.9.40 −0·02 gm. subcutaneously.

Regeneration is calculated on the basis of a maturation time of reticulocytes of 10 hours $\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$. The figures in brackets indicate the destruction if regeneration is calculated on the basis of a maturation time of 24 hours. The figures in the last column represent the total regeneration for the indicated period up to the second date in column 1.

TABLE 2

REGENERATION AND DESTRUCTION OF HAEMOGLOBIN IN PHENYLHYDRAZINE POISONING. RABBIT NO. 17

Date	Regeneration gm. per cent. Hb per day	Gain or loss per day gm. per cent. Hb	Destruction gm. per cent. per day	$\sum\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$
31.7–2.8.40	0·663	−1·45	2·113 (1·726)	1·32
2–5.8.40	2·08	−0·276	2·356 (1·141)	7·54
5–7.8.40	4·55	−0·138	4·688 (2·038)	16·74
7–9.8.40	5·30	+0·76	4·54 (1·45)	27·34
9–12.8.40	3·26	+0·51	2·75 (0·85)	37·12
12–14.8.40	1·34	+0·415	0·925 (0·149)	39·80
14–16.8.40	0·71	−0·415	1·125 (0·711)	41·22
16–19.8.40	0·59	+0·825	−0·235 (−0·579)	42·99
19–21.8.40	0·63	−0·965	1·595 (1·227)	44·25
21–23.8.40	1·11	+0·55	0·56 (−0·083)	46·47
23–24.8.40	1·35	−1·65	3·0 (2·213)	47·82
24–26.8.40	1·12	+0·825	0·295 (−0·352)	50·60
26–28.8.40	0·75	−0·485	1·235 (0·798)	52·1
28–30.8.40	0·41	+0·346	0·064 (−0·175)	52·92
30.8–2.9.40	0·354	−0·276	0·630 (0·423)	53·98
2–4.9.40	0·338	+0·138	0·200 (0·003)	54·68
4–6.9.40	0·595	0·0	0·595 (0·248)	
6–9.9.40	0·63	−0·138	0·867 (0·400)	
9–11.9.40	0·334	+0·276	0·058 (−0·137)	
11–13.9.40	0·405	−0·62	1·025 (0·789)	
13–16.9.40	0.47	+0.138	0·332 (0·058)	
16–18.9.40	0·58	+0·138	0·442 (0·104)	
18–20.9.40	0·77	−0·138	0·908 (0·457)	
20–23.9.40	0·69	+0·276	0·414 (0·011)	
23–27.9.40	0·57	−0·069	0·639 (0·307)	
27.9–2.10.40	0·57	+0·028	0·542 (0·210)	2·84
2–4.10.40	0·775	−2·07	2·845 (2·393)	4·39
4–7.10.40	0·87	+0·276	0·594 (0·086)	6·99
7–9.10.40	0·87	0·0	0·870 (0·362)	8·73
9–11.10.40	1·14	+0·48	0·66 (−0·005)	11·01
11–14.10.40	1·66	+0·76	0·90 (−0·067)	16·01
14–16.10.40	1·16	−0·346	1·506 (0·829)	18·33
16–18.10.40	0·65	0·0	0·65 (0·271)	19·63
18–21.10.40	0·91	0·0	0·91 (0·379)	22·35
21–23.10.40	0·75	0·0	0·75 (0·312)	23·85
23–25.10.40	0·53	+0·485	0·045 (−0·264)	24·91
25–28.10.40	0·50	0·0	0·50 (0·209)	
28–30.10.40	0·385	+0·207	0·178 (−0·101)	
30.10–1.11.40	0·42	+0·276	0·144 (−0·101)	
1–4.11.40	0·288	+0·097	0·191 (0·023)	
4–6.11.40	0·202	−0·276	0·478 (0·360)	
6–8.11.40	0·177	+0·138	0·039 (−0·064)	
8–11.11.40	0·196	+0·20	−0·004 (−0·118)	
11–13.11.40	0·135	−0·50	0·635 (0·556)	
13–15.11.40	0·190	−0·05	0·24 (0·085)	
15–19.11.40	0·498	+0·275	0·223 (−0·671)	
19–21.11.40	0·298	−0·15	0·448 (0·278)	
21–25.11.40	0·254	+0·20	0·054 (−0·094)	
25–27.11.40	0·635	0·0	0·635 (0·264)	
27–29.11.40	0·567	−0·25	0·817 (0·487)	
29.11–2.12.40	0·322	+0·167	0·155 (−0·033)	
2–4.12.40	0·35	−0·95	1·20 (1·096)	

Injections of phenylhydrazine hydrochloride: 31.7.40 −0·02 gm., 5.8.40 −0·02 gm., subcutaneously.

Regeneration is calculated on the basis of a maturation time of reticulocytes of 10 hours $\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$. The figures in brackets indicate the destruction if regeneration is calculated on the basis of a maturation time of 24 hours. The figures in the last column represent the total regeneration in the indicated period up to the second date in column 1.

in tables 1–6 shows that when a maturation time of 24 hours is assumed 44 such impossible figures occur and that even with a maturation time of 10 and 8 hours respectively a few figures with a negative sign are obtained. This suggests that the maturation time determined during the period of high reticulocyte counts is somewhat too long for the period of normal or low reticulocyte counts.

For the study of the kinetics of haemoglobin regeneration summation curves have been constructed (charts VII–XI). In these charts the time in days (for the period under consideration) is plotted against the total haemoglobin intake up to the time (t); $\sum\frac{Hb \times R}{100} \times 2{\cdot}4$ for rabbits and $\sum\frac{Hb \times R}{100} \times 3$ for guinea pigs, obtained by addition of figures in column 2 of tables 1–6.

TABLE 3

REGENERATION AND DESTRUCTION OF HAEMOGLOBIN IN PHENYLHYDRAZINE POISONING. RABBIT NO. 18

Date	Regeneration gm. per cent. Hb per day	Gain or loss per day gm. per cent. Hb	Destruction gm. per cent. per day	$\sum\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$
31.7–2.8.40	0·87	−1·38	2·25 (1·742)	1·74
2–5.8.40	1·92	−0·041	1·961 (0·841)	7·49
5–7.8.40	4·07	−0·346	4·416 (2·046)	15·63
7–9.8.40	4·85	+0·41	4·44 (1·61)	25·33
9–12.8.40	3·78	+0·46	3·32 (1·12)	36·63
12–14.8.40	2·16	+0·138	2·022 (0·762)	40·95
14–16.8.40	1·34	+0·276	1·064 (0·282)	43·63
16–19.8.40	1·07	+0·276	0·794 (0·169)	46·84
19–21.8.40	0·62	+0·138	0·482 (0·120)	48·08
21–23.8.40	0·585	−0·276	0·861 (0·520)	49·25
23–24.8.40	1·27	+0·83	2·10 (−0·295)	
24–26.8.40	1·38	−0·138	1·718 (0·713)	
26–28.8.40	0·92	+0·276	0·644 (0·107)	
28–30.8.40	0·665	+0·138	0·527 (0·139)	
30.8–2.9.40	0·48	−0·41	0·89 (0·61)	
2–4.9.40	0·352	−0·138	0·490 (0·285)	
4–6.9.40	0·463	+0·346	0·117 (−0·153)	
6–9.9.40	0·718	−0·46	1·178 (0·790)	
9–11.9.40	0·765	+0·207	0·558 (0·113)	
11–13.9.40	0·793	+0·276	0·517 (0·054)	
13–16.9.40	1·01	−0·184	1·194 (0·606)	
16–18.9.40	1·04	+0·276	0·764 (0·154)	
18–20.9.40	0·707	0·0	0·707 (0·294)	
20–23.9.40	0·60	0·0	0·60 (0·25)	
23–25.9.40	0·73	+0·138	0·592 (0·166)	1·46
25–27.9.40	0·813	−0·553	1·366 (0·891)	3·086
27.9–2.10.40	1·24	−0·331	1·571 (0·848)	9·286
2–4.10.40	1·72	−0·69	2·41 (1·406)	12·73
4–7.10.40	1·46	+0·316	1·124 (0·294)	17·11
7–11.10.40	1·04	+0·103	0·937 (0·330)	19·2
11–14.10.40	0·686	−0·553	1·239 (0·845)	20·56
14–16.10.40	0·736	+1·51	−0·774 (−1·201)	
16–18.10.40	1·80	−0·62	2·42 (1·37)	
18–21.10.40	2·05	+0·322	1·728 (0·533)	
21–23.10.40	1·35	−0·138	1·488 (0·701)	
23–25.10.40	0·80	−0·276	1·076 (0·610)	
25–28.10.40	0·638	−0·183	0·821 (0·449)	
28–30.10.40	0·607	+0·827	−0·220 (−0·574)	
30.10–1.11.40	0·527	0·0	0·527 (0·220)	
1–4.11.40	0·685	−0·276	0·961 (0·561)	
4–6.11.40	0·398	+0·276	0·122 (−0·110)	
6–8.11.40	0·53	−0·276	0·806 (0·496)	
8–11.11.40	0·95	+0·42	0·53 (−0·026)	
11–13.11.40	0·685	−0·075	0·762 (0·360)	
13–15.11.40	0·48	−0·425	0·905 (0·625)	
15–19.11.40	0·392	+0·1122	0·280 (0·501)	
19–21.11.40	0·372	+0·50	−0·128 (−0·345 !)	
21–25.11.40	0·419	−0·212	0·631 (0·386)	
25–27.11.40	0·775	+0·80	−0·025 (−0·477)	
27–29.11.40	0·82	−0·25	1·07 (0·612)	
29.11–2.12.40	0·65	+0·167	0·483 (0·104)	
2–4.12.40	0·52	−1·05	1·57 (1·265)	

Injections of phenylhydrazine hydrochloride: 31.7.40 −0·02 gm., 5.8.40 −0·02 gm. subcutaneously.

Regeneration is calculated on the basis of a maturation time of reticulocytes of 10 hours $\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$. The figures in brackets indicate the destruction if regeneration is calculated on the basis of a maturation time of 24 hours. The figures in the last column represent the total regeneration for the indicated period up to the second date in column 1.

Such a curve is a real ' haemoglobin intake ' curve and represents the changes in the haemoglobin level which would occur in the absence of cell destruction. The shape of the curves is characteristic and indicates that the ' master reaction ' (Robertson) determining the blood regeneration and haemoglobin intake under these experimental conditions is an autocatalyzed reversible reaction. Mention has been made in the previous paper (part XII) that according to Robertson this is the fundamental reaction for growth and cellular multiplication. The validity of this law for blood regeneration during the reticulocyte response in pernicious anaemia treated with liver extract has been proved by the brilliant work of Riddle (1930). Riddle, however, assumed the actual increase in R.B.C. to be identical

TABLE 4

REGENERATION AND DESTRUCTION OF HAEMOGLOBIN IN PHENYLHYDRAZINE POISONING. RABBIT NO. 20

Date	Regeneration gm. per cent. Hb per day	Gain or loss per day gm. per cent. Hb	Destruction gm. per cent. Hb per day	$\sum\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$
16–18.9.40	1·165	−1·93	3·095 (2·415)	2·33
18–20.9.40	1·73	−1·105	2·835 (1·825)	5·79
20–23.9.40	4·67	−0·138	4·808 (2·088)	19·80
23–25.9.40	5·96	+0·83	5·130 (1·665)	31·72
25–27.9.40	5·52	−1·10	6·620 (3·400)	42·76
27–30.9.40	5·10	+0·735	4·365 (1·385)	58·06
30.9–2.10.40	3·95	+0·69	3·260 (0·955)	65·96
2–4.10.40	2·78	0·0	2·780 (1.160)	71·52
4–7.10.40	1·36	+0·367	0·993 (0·200)	75·60
7–9.10.40	0·47	+0·138	0·332 (0·058)	76·45
9–11.10.40	0·447	−0·138	0·585 (0·324)	77·34
11–14.10.40	0·606	−0·138	0·744 (0·399)	
14–16.10.40	1·235	−0·069	1·304 (0·583)	
16–18.10·40	1·56	−0·276	1·836 (0·926)	
18–21.10.40	1·18	+0·414	0·766 (0·078)	
21–23.10.40	0·83	+0·414	0·416 (−0·069)	
23–26.10.40	0·384	+0·046	0·338 (0·124)	
26–29.10.40	0·538	−0·23	0·762 (0·454)	
29–31.10.40	0·574	+0·069	0·505 (0·170)	
31.10–2.11.40	0·544	−0·346	0·890 (0·570)	
2–4.11.40	0·478	−0·553	1·031 (0·752)	
4–7.11.40	0·397	+0·276	0·121 (−0·111)	
7–9.11.40	0·166	0·0	0·166 (0·069)	
9–12.11.40	0·093	−0·138	0·231 (0·175)	
12–14.11.40	0·072	+0·50	−0·428 (0·470)	
14–16.11.40	0·143	−0·57	0·713 (0·629)	
16–19.11.40	0·63	−0·178	0·808 (0·441)	
19–22.11.40	0·685	+0·243	0·442 (0·042)	
22–25.11.40	0·716	+0·747	−0·031 (−0·652)	
25–27.11.40	1·53	+0·35	1.180 (0·288)	
27–30.11.40	0·867	−0·334	1·201 (0·695)	
30.11–2.12.40	1·36	+0·61	0·750 (−0·040)	
2–4.12.40	1·385	−0·70	2·085 (1·277)	

Injections of phenylhydrazine hydrochloride: 6.9.40 −0·02 gm., 18.9.40 −0·01 gm., 20.9.40 −0·02 gm., 25.9.40 −0·02 gm. subcutaneously.

Regeneration is calculated on the basis of a maturation time of reticulocytes of 10 hours $\left(\frac{Hb \times R}{100} \times 2{\cdot}4\right)$. The figures in brackets indicate the destruction if regeneration is calculated on a basis of a maturation time of 24 hours. The figures in the last column represent the total regeneration up to the second date in column 1.

with the regeneration and the perfect agreement of his observed curves with those calculated from the formula for self accelerated reversible reactions is apparently due to a fixed relation between formation and destruction of R.B.C. in his cases. That this is not always the case even in reticulocyte crises in pernicious anaemia is shown by the work of Goldhammer, Isaacs and Sturgis (1934) and of Schiodt (1938) where the total number of erythrocytes began to increase only after the reticulocytes had reached their peak.

To check the validity of Robertson's law for haemoglobin regeneration in phenylhydrazine anaemia the curves representing the haemoglobin intake $\sum\frac{Hb \times R}{100} \times 2{\cdot}4$ and $\sum\frac{Hb \times R}{100} \times 3$ have been compared with those constructed according to the formula $\log\frac{x}{a-x} = ak(t-t_1)$. If applied to haemoglobin intake, t in this formula is any given time during the period in consideration, t_1 = the time at which 50 per cent. of the total haemoglobin intake of this period has been reached, a = the total haemoglobin intake during this period, x = the expected haemoglobin intake up to the time t, and k is a constant which has been found empirically for each animal and each period. The periods start with the first phenylhydrazine injection when the new stimulus is given and include therefore the days when the haemoglobin is falling. The time when the reticulocyte concentration became fairly constant has been taken as the end point of the period. The curves in the charts VII to XI represent the actual haemoglobin intake

$$\left(\sum\frac{Hb \times R}{100} \times 2{\cdot}4 \quad \text{and} \quad \sum\frac{Hb \times R}{100} \times 3\right)$$

and the intake calculated from the formula for autocatalyzed reversible reactions. In the headings of the charts the individual figures for a and k are given. The curves show perfect agreement between the real haemoglobin intake and that calculated from the formula for self-accelerated reversible reactions. It may be mentioned that the maturation time being taken as constant has no influence on the

TABLE 5

REGENERATION AND DESTRUCTION OF HAEMOGLOBIN IN PHENYLHYDRAZINE POISONING. GUINEA PIG NO. 21.

Date	Regeneration gm. per cent. Hb per day	Gain or loss per day gm. per cent. Hb	Destruction gm. per cent. Hb per day	$\sum\left(\frac{Hb \times R}{100} \times 3{\cdot}0\right)$
18–20.9.40	0·86	−2·35	3·21 (2·627)	1·72
20–23.9.40	0·885	−0·46	1·345 (0·754)	4·37
23–25.9.40	2·60	−0·552	3·152 (1·418)	9·57
25–27.9.40	5·17	+0·345	4·825 (2·070)	19·91
27–30.9.40	5·60	−0·594	6·194 (2·644)	36·71
30.9–2.10.40	5·16	+0·455	4·705 (1·265)	47·03
2–4.10.40	5·30	+0·207	5·093 (1·563)	57·63
4–7.10.40	4·30	+0·73	3·570 (0·707)	70·53
7–9.10.40	1·985	+0·138	1·847 (0·524)	74·34
9–11.10.40	0·985	+0·55	0·435 (−0·223)	76·31
1–14.10.40	0·93	−0·184	1·114 (0·494)	
14–16.10.40	0·99	−0·482	1·472 (0·812)	
16–18.10.40	0·907	−0·276	1·183 (0·578)	
18–21.10.40	1·258	+0·276	0·982 (0·142)	
21–23.10.40	1·435	−0·760	2·195 (1·238)	
23–26.10.40	0·712	+0·555	0·157 (−0·217)	
26–29.10.40	0·234	0·0	0·234 (0·078)	
29–31.10.40	0·515	+0·138	0·377 (0·033)	
31.10–2.11.40	0·585	0·0	0·585 (0·195)	
2–4.11.40	0·61	−0·276	0·886 (0·479)	
4–7.11.40	0·59	−0·092	0·682 (0·288)	
7–9.11.40	0·358	−0·55	0·908 (0·430)	
9–12.11.40	0·165	+0·230	−0·065 (0·175)	
12–14.11.40	0·678	−0·125	0·803 (0·351)	
14–16.11.40	1·29	−0·350	1·640 (0·780)	
16–19.11.40	1·62	+0·273	1·347 (0·266)	
19–22.11.40	1·18	+0·100	1·080 (0·393)	
22–25.11.40	1·88	+0·233	1·647 (0·395)	
25–27.11.40	2·20	+0·60	1·600 (0·133)	
27–30.11.40	0·49	+0·100	0·390 (0·063)	
30.11–2.12.40	0·234	+0·300	−0·066 (−0·222)	
2–4.12.40	0·208	−0·735	0·943 (0·805)	

Injections of phenylhydrazine hydrochloride: 18.9.40 −0·01 gm., 20.9.40 −0·01 gm., 25.9.40 −0·01 gm., 27.9.40 −0·02 gm. subcutaneously.

Regeneration is calculated on the basis of a maturation time for reticulocytes of 8 hours $\left(\frac{Hb \times R}{100} \times 3{\cdot}0\right)$. The figures in brackets indicate the destruction if regeneration is calculated on the basis of a maturation time of 24 hours. The figures in the last column represent the total regeneration up to the second date in column 1.

shape of the curve. The agreement indicates that in phenylhydrazine anaemia the mass of erythrocytes (and therefore haemoglobin) liberated from the bone marrow is absolutely determined by the law of nuclear synthesis, that is by the multiplication of nucleated R.B.C. in the bone marrow. No delay was detected in the development of the regenerative response. This finding is strongly against there being any toxic action of phenylhydrazine on the bone marrow as was assumed from cytological findings by Price Jones (1911–12). These findings may rather be interpreted as indicating increased and precipitate erythropoiesis for macro-blasts and pro-erythroblasts (Price Jones's megaloblasts and metrocytes *) are commonly found in the bone marrow of congenital acholuric jaundice and Istomanowa (1926) found signs of great activity in the bone marrow in pyrodin (acetyl phenylhydrazine) intoxication. Evensen (1938) who studied the effects of phenylhydrazine in polycythaemia found no signs of inhibition of the bone marrow. The drop in haemoglobin and R.B.C. which persists for some days after the last phenylhydrazine injection is therefore to be attributed to the destruction of R.B.C.

It is by no means justifiable to draw general conclusions as to the mechanism of red cell regeneration from findings of anaemia produced by a noxious agent like phenylhydrazine. It is important therefore to analyse the haemoglobin or erythrocyte regeneration in post-haemorrhagic anaemia and especially in conditions in which a normal mechanism of regeneration may reasonably be assumed. No experiments have been made on post-haemorrhagic anaemia but in the vast literature on this subject sufficient data for the construction of regeneration curves has been found in a paper by Gordon (1934). One of his experiments has been chosen in which five rabbit litter mates were subjected to a single bleeding and the average of the figures given for these five animals has been taken (table 7). As the maturation time, which with little error may be taken as constant, has no influence on the shape of

* The term 'metrocytes' was introduced by Engel for those nucleated red cells of early embryonic life which are called megaloblasts by most authors. The differentiation between 'primary metrocytes,' 'secondary metrocytes' and megaloblasts is based only on the staining properties of the protoplasm.

TABLE 6

REGENERATION AND DESTRUCTION OF HAEMOGLOBIN IN PHENYLHYDRAZINE POISONING. GUINEA PIG. NO. 22

Date	Regeneration gm. per cent. Hb per day	Gain or loss per day gm. per cent. Hb	Destruction gm. per cent. Hb per day
18–20.9.40	1·055	−0·138	1·193 (0·490)
20–23.9.40	1·64	−1·75	3·390 (2.297)
23–25.9.40	4·07	−0·276	4·346 (1·630)
25–27.9.40	8·42	+0·30	8·120 (2·510)
27–39.9.40	10·15	−0·30	10·450 (3·680)
30.9–2.10.40	7·68	+0·552	7·128 (2·008)
2–4.10.40	4·85	+0·415	4·435 (0·800)
4–7.10.40	4·28	+0·597	3·683 (0·828)
7–9.10.40	2·478	−0·138	2·616 (0·963)
9–11.10.40	1·038	−0·552	1·590 (0·898)
11–14.10.40	0·992	+0·597	0·395 (−0·206)
14–16.10.40	1·128	−0·207	1·335 (0·583)
16–18.10.40	0·969	−0·414	1·383 (0·737)
18–21.10.40	0·897	+0·552	0·345 (−0·257)
21–23.10.40	0·924	−0·069	0·993 (0·377)
23–26.10.40	0·542	+0·046	0·496 (0·105)
26–29.10.40	0·595	+0·189	0·406 (0·009)
29–31.10.40	0·72	−1·04	1·760 (1·280)
31.10–2.11.40	0·78	+1·38	−0·600 (−1·120)
2–4.11.40	1·54	−0·138	1·678 (0·651)
4–7.11.40	1·25	−0·092	1·342 (0·505)
7–9.11.40	0·35	−0·276	0·626 (0·393)
9–12.11.40	0·521	+0·46	0·061 (−0·282)
12–14.11.40	0·62	−0·276	0·896 (0·483)
14–16.11.40	0·652	+0·100	0·552 (0·118)
16–19.11.40	0·683	+0·333	0·350 (0·102)
19–22.11.40	0·384	−0·333	0·717 (0·461)
22–25.11.40	0·382	+0·300	0·082 (−0·173)
25–27.11.40	0·382	0·0	0·382 (0·127)
27–30.11.40	0·266	+0·100	0·166 (−0·011)
30.11–2.12.40	0·176	−0·250	0·426 (0·309)
2–4.12.40	0·342	−1·00	1·342 (1·114)

Injections of phenylhydrazine hydrochloride: 18.9.40 −0·01 gm., 20.9.40 −0·01 gm., 25.9.40 −0·01 gm., 27.9.40 −0·02 gm. subcutaneously.

Regeneration is calculated on the basis of a maturation time for reticulocytes of 8 hours $\left(\frac{Hb \times R}{100} \times 3{\cdot}0\right)$. The figures in brackets indicate the destruction if regeneration is calculated on the basis of a maturation time of 24 hours.

TABLE 7

REGENERATION AND DESTRUCTION OF R.B.C. IN POST-HAEMORRHAGIC ANAEMIA

Days of experiment	R.B.C. millions per c.mm.	Reticulocytes per cent.	Daily intake of R.B.C. millions per c.mm.	Daily gain in R.B.C. millions per c.mm.	Daily destruction of R.B.C. millions per c.mm.
Pre-experimental	6·07	0·58	0·0767	0	0·0767 (0·032)
2–3	4·235	1·75	0·178	0·07	0·108
3–4	4·31	3·3	0·342	0·1	0·242
4–5	4·36	4·95	0·518	0	0·518
5–6	4·37	6·3	0·663	0·02	0·643 (0·256)
6–7	4·39	6·33	0·67	0·02	0·650 (0·259)
7–8	4·405	4·9	0·52	0·01	0·510
8–9	4·43	3·8	0·405	0·04	0·365
9–10	4·595	3·38	0·40	0·29	0·11
10–12	4·80	3·02	0·347	0·06	0·287
12–14	4·94	2·51	0·298	0·08	0·218
14–17	5·095	2·04	0·249	0·05	0·199
17–24	5·545	1·57	0·208	0·107	0·101
24–31	5·995	1·02	0·144	0·0214	0·123

The daily intake is calculated on the basis of a maturation time of reticulocytes of 10 hours : $\frac{E \times R}{100} \times 2{\cdot}4$. The figures in brackets correspond to the daily destruction if a maturation time of 24 hours is assumed for the reticulocytes

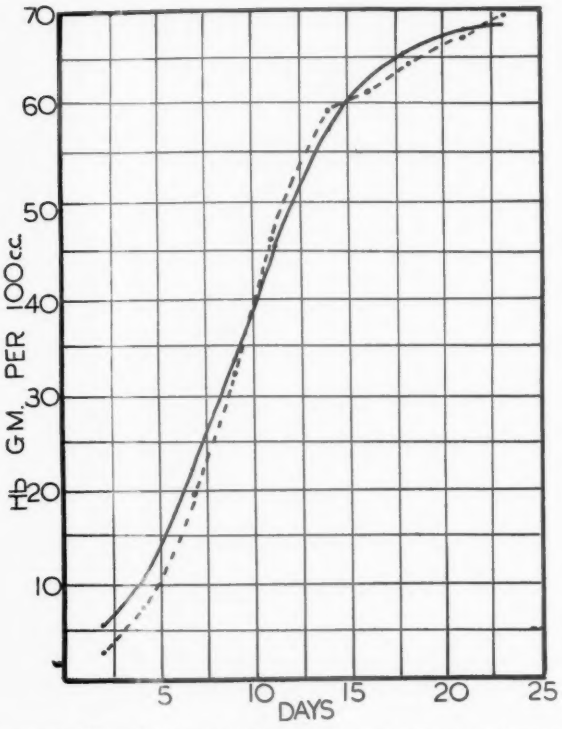

CHART VII.—Haemoglobin intake in phenylhydrazine anaemia of rabbit No. 15, 29.7–21.8.1940.

——— calculated from the equation $\log \frac{x}{69{\cdot}5-x} = 0{\cdot}00208 \times 69{\cdot}5(t-9{\cdot}3)$. – – – – – – – observed figures for $\sum \frac{Hb \times R}{100} \times 2{\cdot}4$.

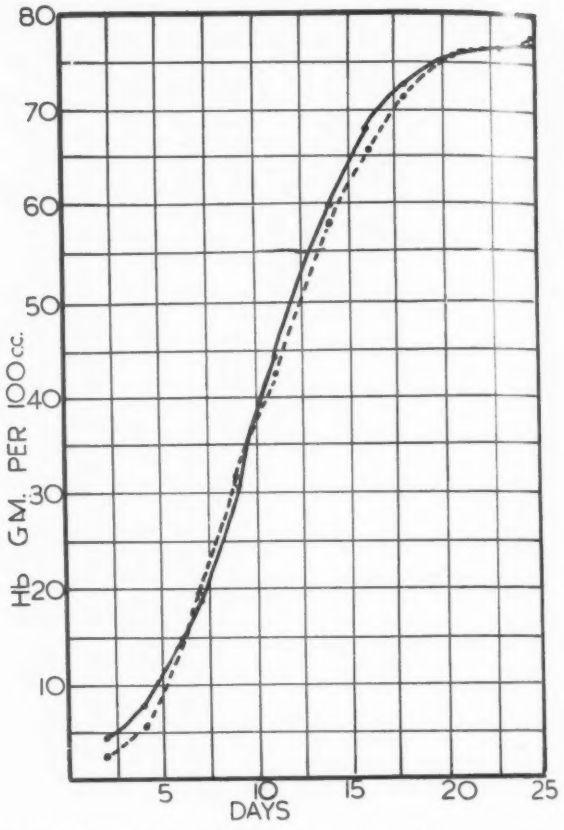

CHART IX.—Haemoglobin intake in phenylhydrazine anaemia of rabbit No. 20, 16.9–11.10.1940.

——— calculated from the equation $\log \frac{x}{77{\cdot}34-x} = 0{\cdot}00194 \times 77{\cdot}34(t-10{\cdot}26)$. – – – – – – – observed figures for $\sum \frac{Hb \times R}{100} \times 2{\cdot}4$.

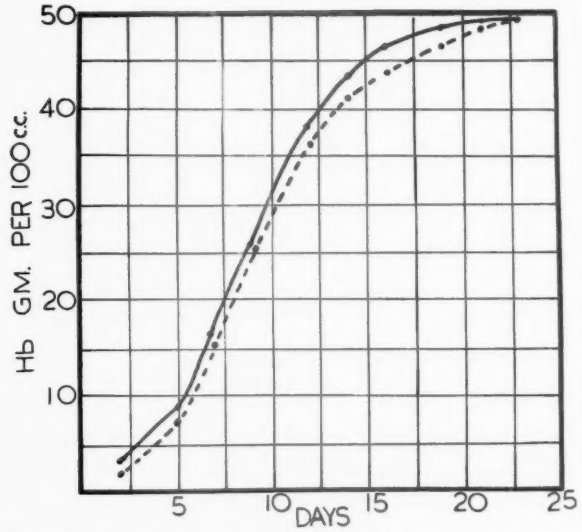

CHART VIII.—Haemoglobin intake in phenylhydrazine anaemia of rabbit No. 18, 31.7–23.8.1940.

——— calculated from the equation $\log \frac{x}{49{\cdot}25-x} = 0{\cdot}00346 \times 49{\cdot}25(t-8{\cdot}86)$. – – – – – – observed figures for $\sum \frac{Hb \times R}{100} \times 2{\cdot}4$.

the curve the formula $\sum \frac{E \times R}{100}$ (where E = R.B.C.) corresponding to a maturation time of 24 hours has been used for the construction of chart XII. If this curve (solid line) is compared with the theoretical one corresponding to the formula $\log \frac{x}{1{\cdot}667-x} = 0{\cdot}19 \times 1{\cdot}667(t-5{\cdot}7)$ (dashed line) an agreement as perfect as that in the case of phenylhydrazine anaemia will be found.

A condition in which it may be fairly assumed that the mechanism of the regeneration is normal has been met in rabbits previously subjected to phenylhydrazine-poisoning. After complete recovery, even some weeks later, the sudden 'spontaneous' development of anaemia has been observed, the cause of which is discussed below. The development of anaemia was always followed by a reticulocyte response and recovery. The haemoglobin intake during such periods and the theoretical one calculated from the formula for autocatalyzed reversible reactions are represented in charts XIII to XVI for rabbits 15, 17 and 18 and for guinea pig 21.

Finally the same analysis of regeneration has been

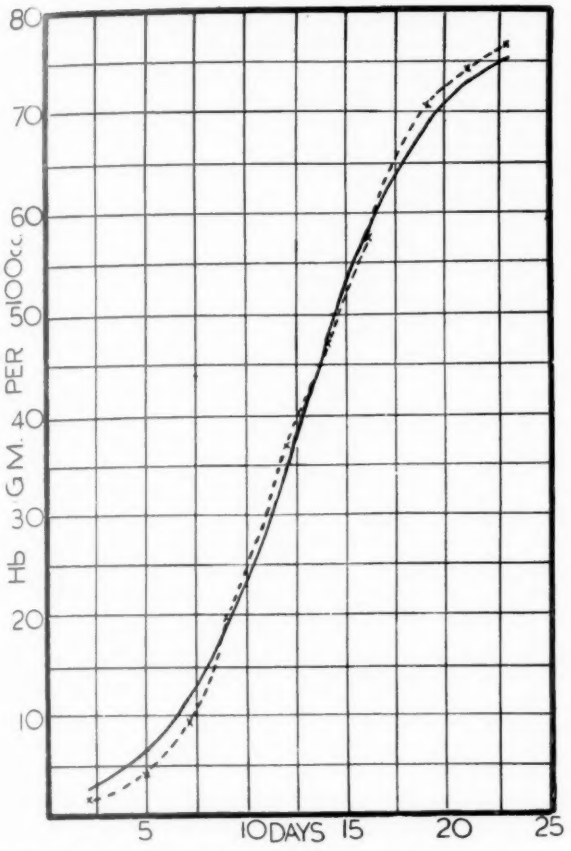

CHART X.—Haemoglobin intake in phenylhydrazine anaemia of guinea pig No. 21, ———— calculated from formula: $\log \frac{x}{78{\cdot}7-x} = 0{\cdot}00173 \times 78{\cdot}17(t-12{\cdot}635)$. – – – – – observed figures for $\sum \frac{Hb \times R}{100} \times 2{\cdot}4$.

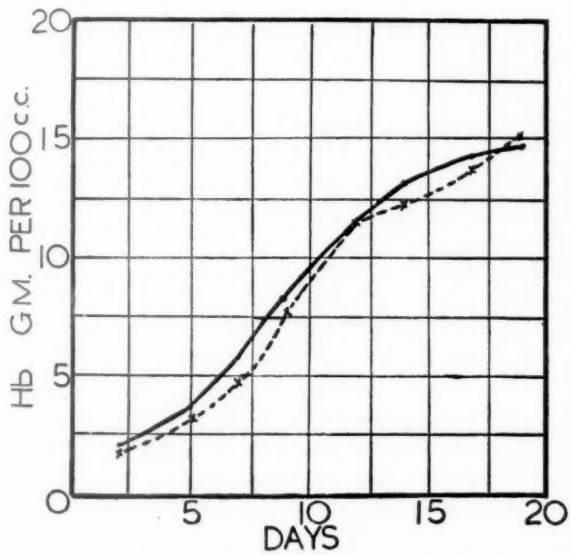

CHART XI.—Haemoglobin intake in phenylhydrazine anaemia of guinea pig No. 22, ———— calculated from equation: $\log \frac{x}{15{\cdot}1-x} = 0{\cdot}00966 \times 15{\cdot}1(t-8{\cdot}43)$. – – – – – observed figures for $\sum \frac{Hb \times R}{100} = 3{\cdot}0$.

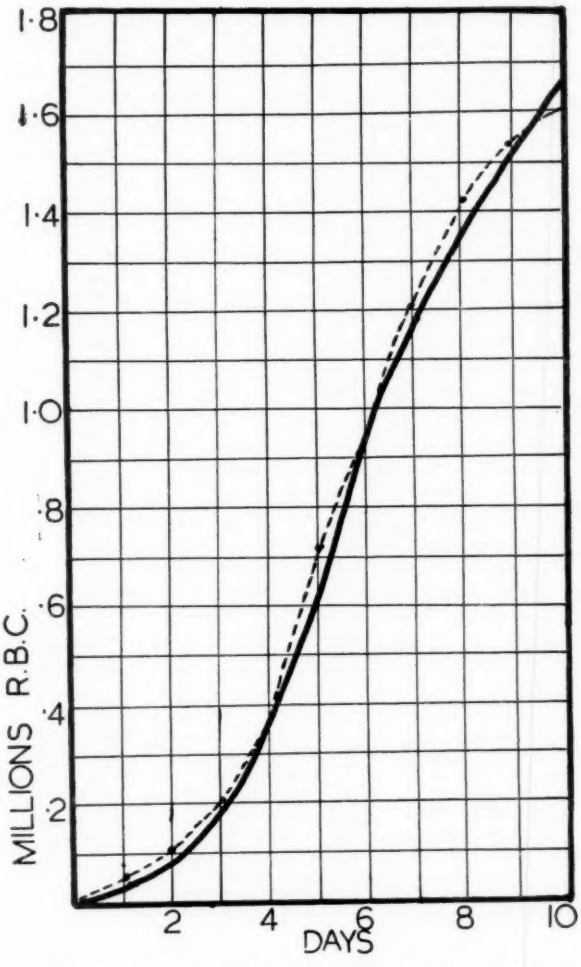

CHART XII.—Haemoglobin intake in post-haemorrhagic anaemia of rabbits. ———— observed figures for $\sum \frac{E.R}{100}$. – – – – – calculated from the formula: $\log \frac{x}{1{\cdot}667-x} = 0{\cdot}19 \times 1{\cdot}667(t-5{\cdot}7)$. Constructed from figures of Gordon.

applied to a case of erythronoclastic anaemia of the newborn. In this case, which because of various interesting features will be discussed in detail below, repeated transfusions resulted in an ' aregenerative ' condition of the bone marrow which was succeeded by a period of renewed bone marrow activity. The maturation time determined in vitro during this period was 11½ hours. A time of 12 hours was used for the construction of curve 17 which therefore represents $\sum \frac{Hb \times R}{100} \times 2$ (dashed curve). The theoretical curve corresponds to the formula: $\log \frac{x}{13{\cdot}27-x} = 0{\cdot}0215 \times 13{\cdot}27(t-6{\cdot}47)$ (solid line). The agreement between the two curves is again very close.

Graphs give only a rough idea of agreement; they are influenced by the scale which for technical reasons could not be identical in all cases. For a more accurate comparison of observed figures for haemoglobin intake with those calculated from the formula for autocatalyzed reversible reactions the

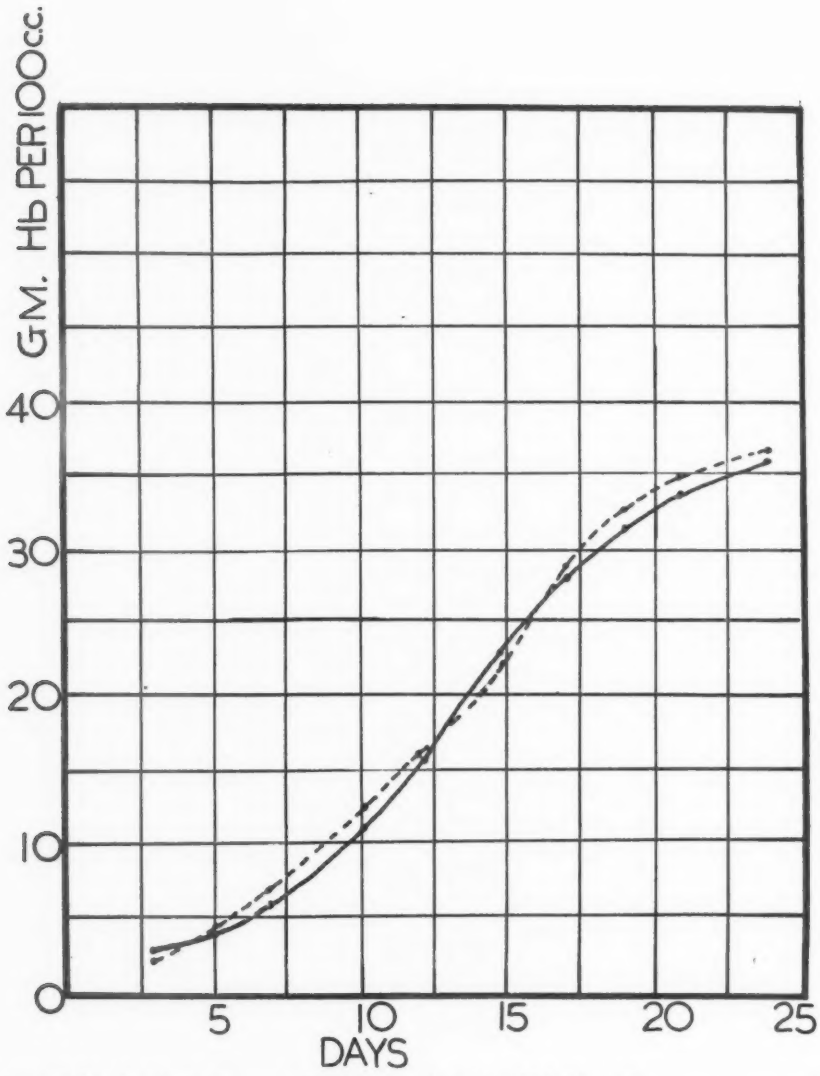

CHART XIII.—Haemoglobin intake in 'spontaneous anaemia' of rabbit No. 15. ———— calculated from the formula: $\log \frac{x}{37{\cdot}85-x}=0{\cdot}117(t-13{\cdot}32)$. – – – – – observed figures for $\sum\frac{Hb\times R}{100}\times 2{\cdot}4$.

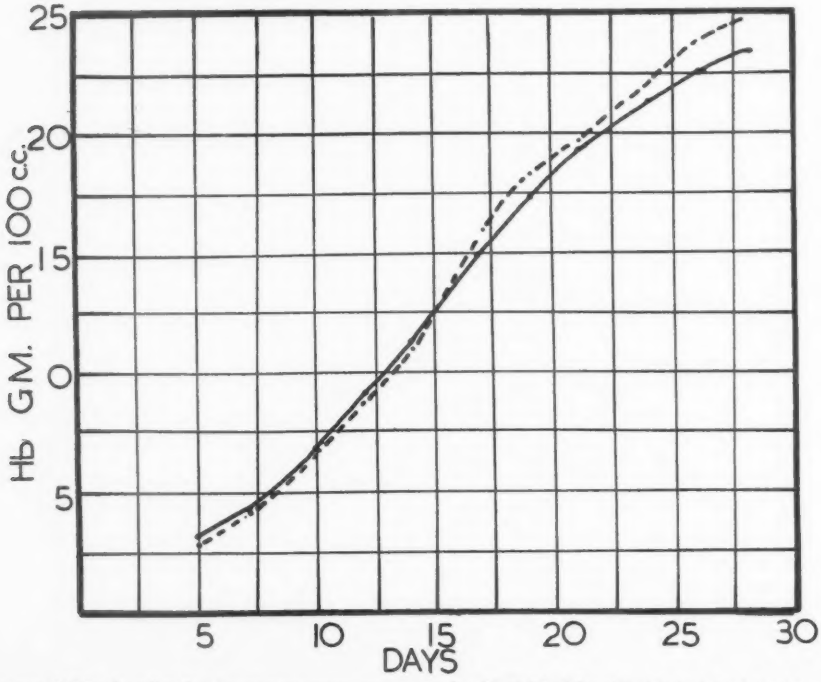

CHART XIV.—Haemoglobin intake in 'spontaneous anaemia' of rabbit No. 17, 27.9–25.10.1940. ——— calculated from the equation: $\log \frac{x}{24{\cdot}91-x}=0{\cdot}00342\times 24{\cdot}91(t-14{\cdot}875)$. – – – – – – – observed figures for $\sum\frac{Hb\times R}{100}\times 2{\cdot}4$.

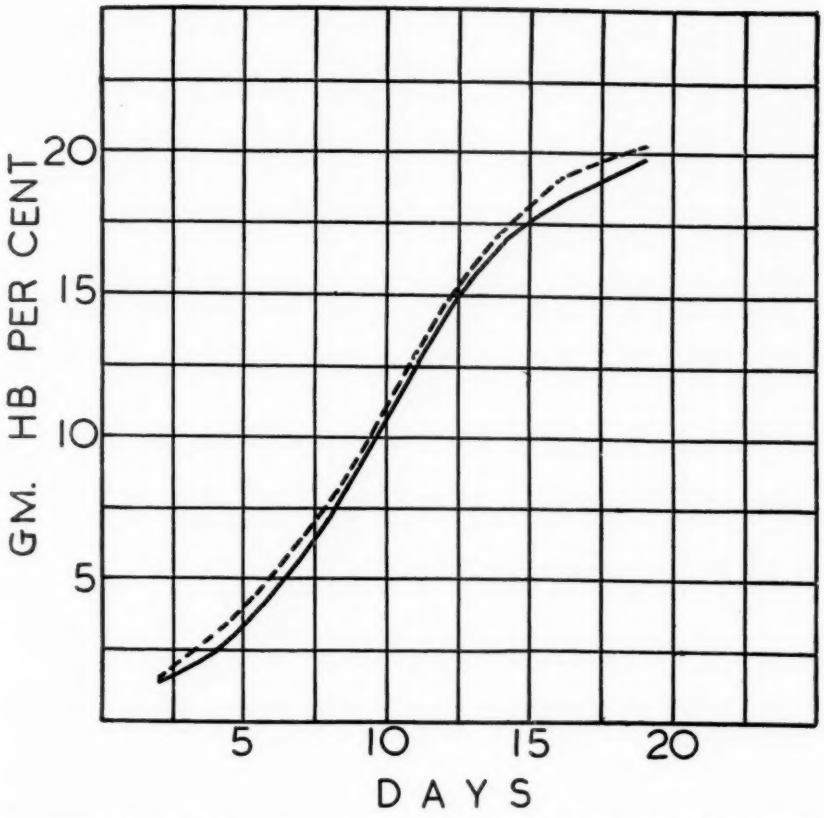

CHART XV.—Haemoglobin intake in 'spontaneous anaemia' of rabbit No. 18, 23.9–14.10.1940. ——— calculated from formula: $\log \frac{x}{20{\cdot}56-x}=0{\cdot}00732\times 20{\cdot}56(t-9{\cdot}67)$. – – – – Observed figures for $\sum\frac{Hb\times R}{100}\times 2{\cdot}4$.

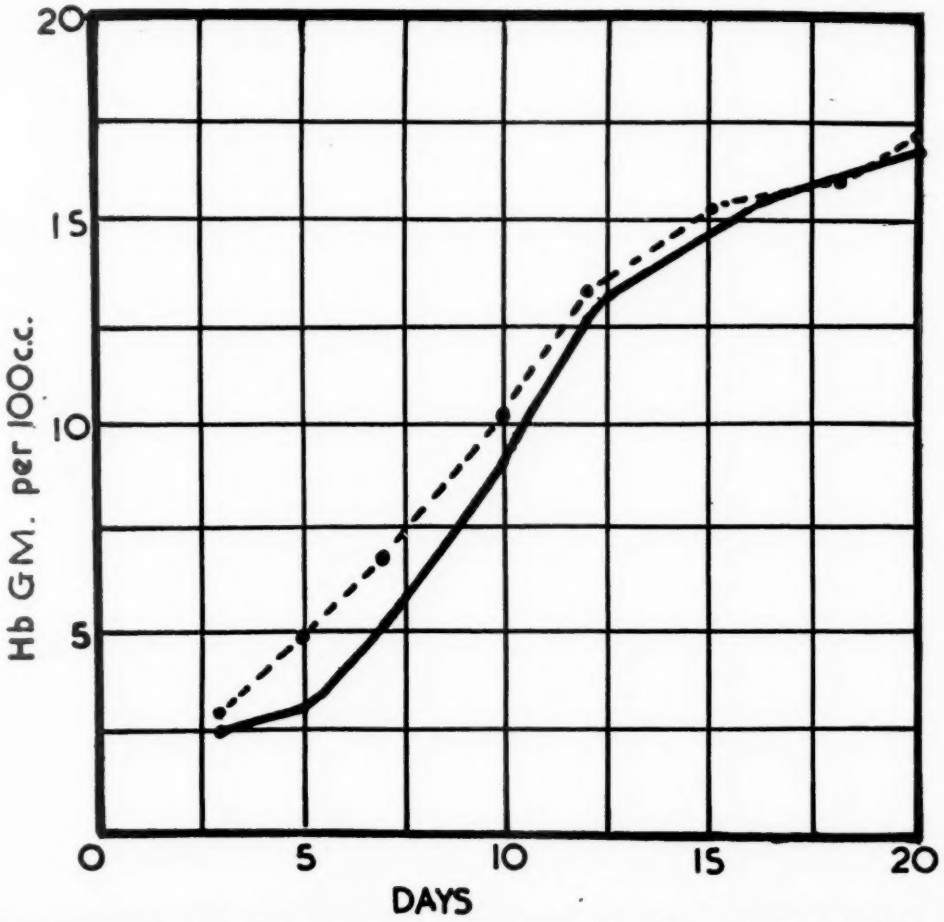

CHART XVI.—Haemoglobin intake in 'spontaneous anaemia' of guinea pig No. 21 (11–31.10.1940). ——— calculated from formula: $\log \frac{x}{17{\cdot}12-x}=0{\cdot}00876\times 17{\cdot}12(t-9{\cdot}5)$. – – – – – Observed figures for $\sum\frac{Hb\times R}{100}\times 3{\cdot}0$.

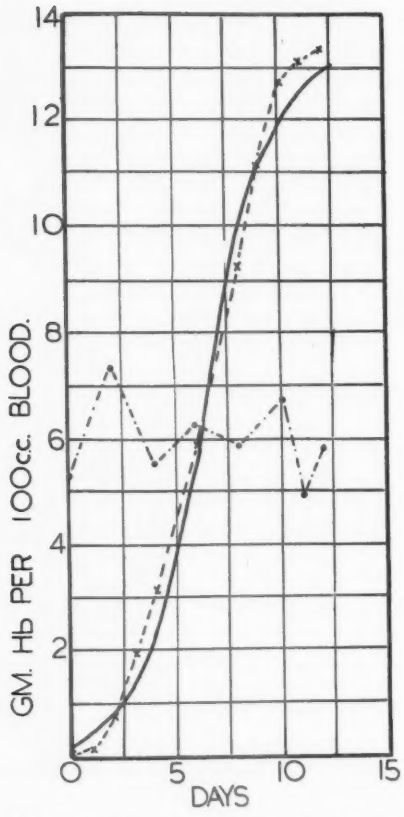

CHART XVII.—Haemoglobin intake and variations in the haemoglobin level in a case of erythronoclastic anaemia of the newborn (Baby K.H.).—.—.— Variations in the haemoglobin level. – – – – – Observed figures for $\sum \frac{Hb \times R}{100} \times 2{\cdot}0$. ——— Haemoglobin intake calculated from the formula: $\log \frac{x}{13{\cdot}27 - x} = 0{\cdot}0215 \times 13{\cdot}27(t - 6{\cdot}47)$.

calculation of the constant according to the procedure of Robertson and the divergence between the observed and calculated values of x (haemoglobin intake) in the case of phenylhydrazine anaemia and of 'spontaneous anaemia' of rabbit 15 are given in tables 8–11. On the basis of figures given in tables 1–6 the same calculation can be made for all animals and all periods.

Discussion

From the foregoing the following conclusion may be drawn. Whatever may be the stimulus to increased erythrocyte and haemoglobin formation the liberation of R.B.C. from the blood-forming organs follows the kinetics of autocatalyzed reversible reactions and is therefore exclusively determined by the process of the multiplication of nucleated cells in the bone marrow.

In the course of blood disorders periods of increasing and decreasing bone marrow activity alternate with periods of equilibrium. The word equilibrium is used here to indicate a state of bone marrow activity resulting in the output of a constant mass of red cells each day without necessarily any relation to the rate of peripheral red cell destruction and may therefore be associated with a constant red cell level, with a fall or with a rise. The only characteristic feature of such a state is the constant reticulocyte concentration; the points for $\sum \frac{Hb \times R}{100} \times k$ fall therefore on a straight line. Alternation of periods of increased erythropoietic activity with periods of equilibrium results in a characteristic curve such as shown in chart XVIII where $\sum \frac{Hb \times R}{100} \times 2{\cdot}4$ is represented over a period of 32 days. This curve shows striking resemblance to the

TABLE 8

HAEMOGLOBIN REGENERATION IN PHENYLHYDRAZINE-ANAEMIA OF RABBIT NO. 15.

Calculation of the constant K(=k.A). A = the total intake of haemoglobin over the 'cycle,' x = the observed haemoglobin intake up to the time t, t_1 = the time when $x = \frac{A}{2}$, which is in this case 9·352 days. Values for $K(t - t_1)$ corresponding to the observed values for $\frac{x}{A}$ are taken from the table of Robertson.

Days	x	$\frac{x}{A}$	$K(t - t_1)$	$t - t_1$	K
2	2·784	0·040	−1·380	−7·352	0·188
4	7·89	0·113	−0·895	−5·352	0·168
7	19·60	0·282	−0·406	−2·352	0·173
9	32·30	0·465	−0·061	−0·352	0·173
11	46·20	0·665	+0·298	+1·648	0·182
14	59·50	0·857	+0·778	+4·648	0·167
16	61·60	0·887	+0·895	+6·648	0·135
18	64·30	0·925	+1·091	+8·648	0·126
21	67·80	0·975	+1·591	+11·648	0·136
				Average	0·161

TABLE 9

HAEMOGLOBIN REGENERATION IN PHENYLHYDRAZINE-ANAEMIA OF RABBIT NO. 15

Comparison of the observed values for haemoglobin intake (x) with those calculated from the formula for autocatalyzed reactions: $\log \frac{x}{69{\cdot}50 - x} = 0{\cdot}161(t - 9{\cdot}352)$. The figures in column 2 are obtained by multiplying the observed values for $t - t_1$ with 0·161. The corresponding values for $\frac{x}{A}$ are taken from the table of Robertson.

Days	$K(t - t_1)$ calculated	$\frac{x}{A}$ calculated	x calculated	x observed	Divergence
2	−1·180	0·062	4·300	2·784	−1·516
4	−0·862	0·121	8·41	7·89	−0·52
7	−0·378	0·295	20·40	19·60	−0·80
9	−0·056	0·467	32·20	32·30	+0·10
11	+0·268	0·650	45·20	45·20	+1·00
14	+0·746	0·848	58·90	59·50	+0·60
16	+1·070	0·922	64·00	61·60	−2·40
18	+1·390	0·961	66·60	64·30	−2·30
21	+1·875	0·987	68·50	67·8	−0·70

growth-curve of man with its two or three periods of accelerated growth as reproduced by Robertson (1923) and by Brock (1932).

TABLE 10

HAEMOGLOBIN REGENERATION IN 'SPONTANEOUS ANAEMIA' OF RABBIT NO. 15

Calculation of the constant K(=k.A). A=the total haemoglobin intake over the 'cycle,' x=the observed haemoglobin intake up to the time t, t_1=the time when $x=\frac{A}{2}$, which is in this case 13·32 days. Values for $K(t-t_1)$ corresponding to the observed values of $\frac{x}{A}$ are taken from the table of Robertson.

Days	x	$\frac{x}{A}$	$K(t-t_1)$	$t-t_1$	K
3	2·22	0·059	−1·203	−10·32	0·116
5	4·28	0·113	−0·895	−8·32	0·108
7	6·96	0·184	−0·647	−6·32	0·102
10	12·84	0·339	−0·290	−3·32	0·088
12	16·04	0·423	−0·135	−1·32	0·102
14	20·40	0·539	−0·068	+0·68	0·100
17	28·80	0·761	+0·503	+3·68	0·136
19	32·78	0·866	+0·810	+5·68	0·152
21	34·82	0·920	+1·061	+7·68	0·138
24	36·59	0·960	+1·380	+10·68	0·129
				Average	0·117

TABLE 11

HAEMOGLOBIN REGENERATION IN 'SPONTANEOUS ANAEMIA' OF RABBIT NO. 15

Comparison of the observed values for haemoglobin intake (x) with those calculated from the formula for autocatalyzed reactions: $\log\frac{x}{37·85-x}=0·117(t-13·32)$. The figures in column 2 are obtained by multiplying the observed value for $t-t_1$ with 0·117. The corresponding values for $\frac{x}{A}$ are taken from the table of Robertson.

Days	$K(t-t_1)$ calculated	$\frac{x}{A}$ calculated	x calculated	x observed	Divergence
3	−1·209	0·070	2·66	2·22	−0·44
5	−0·972	0·096	3·63	4·28	+0·65
7	−0·739	0·154	5·84	6·96	+1·12
10	−0·338	0·291	11·00	12·84	+1·84
12	−0·154	0·412	15·61	16·04	+0·53
14	+0·080	0·546	20·70	20·40	−0·30
17	+0·430	0·729	27·60	28·80	+1·20
19	+0·665	0·822	31·20	32·78	+1·58
21	+0·900	0·888	33·70	34·82	+1·12
24	+1·250	0·947	36·00	36·59	+0·59

The rise in haemoglobin and erythrocytes during recovery from anaemia, however, is determined by a second factor besides the release of R.B.C. from

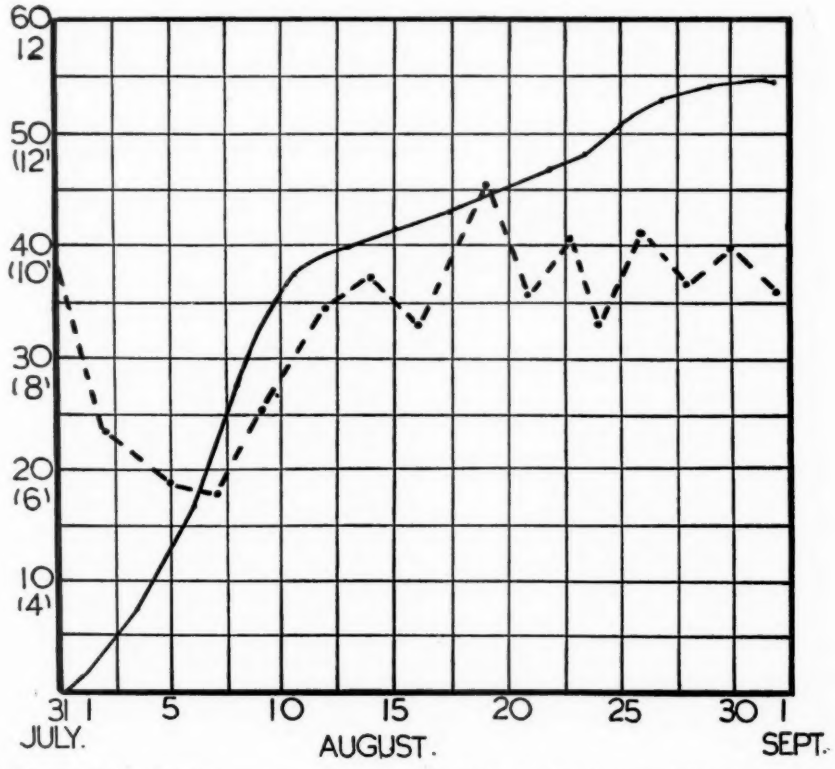

CHART XVIII.—Haemoglobin intake (————) and variations in the haemoglobin level (– – – – –) of rabbit No. 17 for a period of 32 days. The solid line represents the summation curve $\sum\frac{Hb\times R}{100}\times 2·4$, the figures on the y-axis are gm. haemoglobin per 100 c.c. of circulating blood; the figures in brackets correspond to the dashed curve which represents the observed haemoglobin levels in gm. per 100 c.c.

the bone marrow, namely the destruction of circulating cells. Chart XVII shows that periods may occur when the haemoglobin intake takes a course corresponding with that after a single stimulus with perfect agreement with the curve of autocatalyzed reactions and the haemoglobin levels show only irregular and independent variations. It is not correct to call a curve representing the rise in haemoglobin or erythrocytes a ' regeneration curve ' and in this paper it will be called a curve of repair or recovery. The interplay of the two factors, formation and destruction, results in such variations of the curve of repair as have been mentioned above and this curve may show not the slightest resemblance to a curve of autocatalyzed reversible reactions. Theoretically repair is possible without a change in the regeneration if a reduction of the destruction rate occurs; there is, however, no evidence for such an event. What part is really played by the factor of reduced destruction can only be determined if curves of regeneration or intake are compared with those of repair and figures for intake with those of destruction. The figure for haemoglobin destruction per 100 c.c. circulating blood are given in column 4 of tables 1–6. The normal haemoglobin destruction, which equals the normal intake, has been calculated from the formula for daily haemoglobin intake $\frac{Hb \times R}{100} \times 2{\cdot}4$, on the basis of forty counts on twenty-one rabbits. The mean daily haemoglobin destruction per 100 c.c. blood has thus been found to be 0·676 gm. haemoglobin daily with a standard deviation of 0·254 gm. The corresponding figures for guinea pigs calculated from twenty-five counts on seven animals were 0·625 and 0·398 respectively. It will be seen from the figures for the standard deviation that the normal variation is very high, the coefficient of variation being 37·6 per cent. for rabbits and 63·5 per cent. for guinea pigs. This makes it impossible to decide by means of statistical rules whether a reduction in the destruction quota is significant or not and an

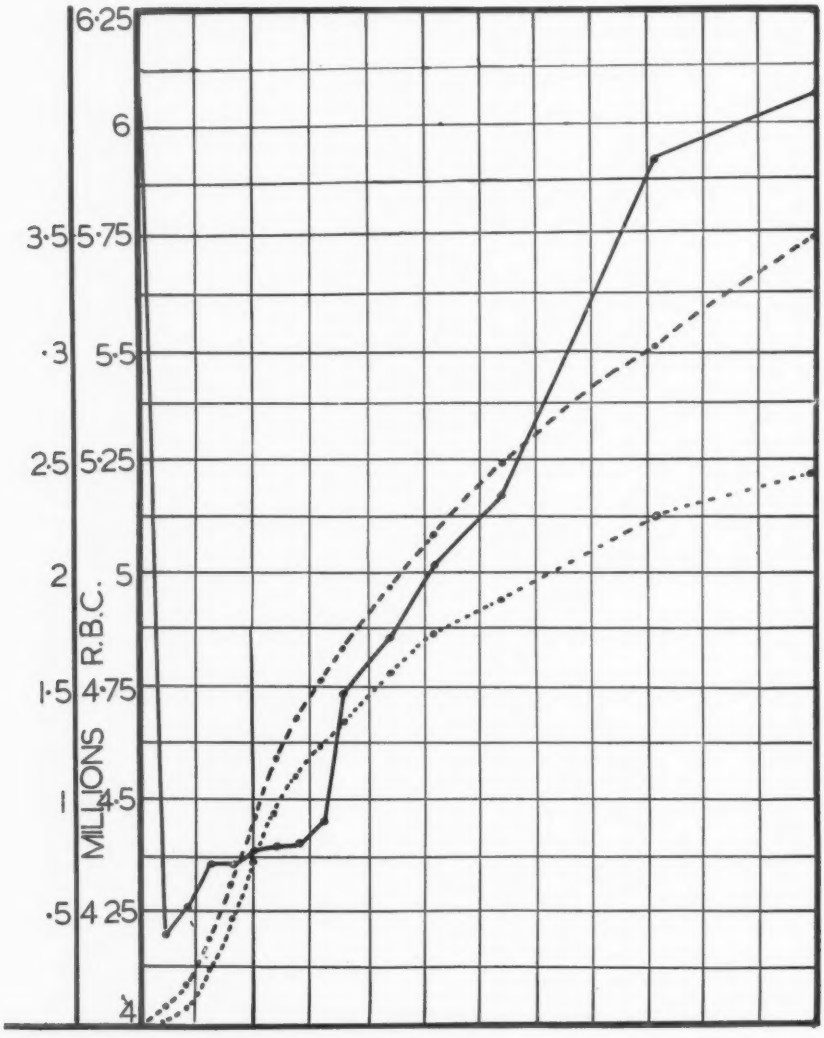

CHART XIX.—Blood regeneration in post-haemorrhagic anaemia. Constructed from the figures of Gordon. ———— Red blood corpuscles. – – – – – – Intake of R.B.C. $\left(\sum \frac{E.R}{100}\right)$. . . . . Excess in the intake of R.B.C. $\left[\sum\left(\frac{E.R}{100} - \frac{E.R}{100}\right)\right]$.

arbitrary description of the reduction as being marked or slight is all that is possible.

In charts XVIII and XIX regeneration or haemoglobin intake curves can be compared with those of repair for phenylhydrazine anaemia and for haemorrhagic anaemia. From study of these curves and comparison of the figures in column 4 of tables 1–6 and column 5 in table 7 with the normal haemoglobin destruction it will be seen that during the early stage of recovery from both phenylhydrazine anaemia and post-haemorrhagic anaemia the destruction of R.B.C. is considerably increased. The rise in haemoglobin therefore at this time is due only to excess formation. In the later stages, however, periods of decreased destruction are met; they are much shorter than those of increased intake, a considerable reduction of haemoglobin destruction lasting only a few days. This suggests that the destruction of R.B.C. is a vitally important event. The reasons for this importance remain a mystery. Observations of Patek and Minot (1934), Parsons (1938), Verzar and collaborators (1929), Fellinger (1932) and recently Bomford (1940) indicate the importance of haemoglobin derivatives in blood formation. It may be that bilirubin and stercobilin exert a hormone-like action in erythropoiesis but other functions also are possible.

While short in duration and rarely considerable yet the reduction of blood destruction appears to be responsible for some part of the recovery in some cases. Charts I, II, VI and XIX show that in the later stages of recovery there are periods when a rise in haemoglobin occurs in a stage of bone marrow equilibrium (points for $\sum \frac{Hb \times R}{100} \times k$ falling on a straight line, reticulocyte counts constant and not increased). This rise may sometimes be even as steep as that in the period of greatest bone marrow activity.

Analysis of blood regeneration in experimental anaemia leads to the following conclusions:

Every appreciable drop in haemoglobin is a stimulus which provokes increased activity in the blood forming organs. This increased activity follows the kinetics of autocatalyzed reversible reactions. The haemoglobin intake is a precise reproduction of this reaction in the bone marrow. The real increase in haemoglobin is modified by changes in the destruction and the latter is always increased at the beginning of repair and often in the later stages also. A reduction in blood destruction has been observed only for short periods, but it may be responsible for some increase in the haemoglobin.

It has been shown that a straight line of repair after loss of blood is only due to the interference of blood destruction. An explanation by so simple a mechanism as is assumed by Schiodt is therefore not justifiable and estimation of the life span of erythrocytes from the time of repair is not conclusive. Difficulty also arises in determining the time of repair. In phenylhydrazine anaemia, and in anaemia from bleeding as well, a haemoglobin level is often reached higher than the pre-experimental one while in other cases under identical experimental conditions the recovery comes to a standstill at a lower haemoglobin level than was present at the start. How few conclusions can be drawn from the time of repair and how complicated is the final mechanism of repair is particularly evident from experiments where the regeneration took place with a damaged bone marrow. Thus in the experiments of Gottlebe and Skibbe (1936) anaemia was produced by saponin or saponin plus electro-collargol. Whenever injections were stopped there was a sharp rise in the red cell count for a few days, but afterwards it remained constant for about two weeks and the total time of repair was some sixty to seventy days. Liver extract injected during the period of constant R.B.C. level resulted in a reticulocyte response and a rise in the number of erythrocytes but, after a few days, the count returned to its previous figure and the total time of repair was not shortened.

The interplay of increased destruction and formation results in many experiments, for reasons which it does not seem possible to explain, in a duration of the time of repair which corresponds closely to the life span of erythrocytes as determined by more reliable methods. Thus the time of repair from phenylhydrazine anaemia in the rabbit was 12, 13, 19 and 23 days respectively, an average of 16·7 days, whereas the life span calculated from the average reticulocyte count of 2·7 per cent. and a maturation time of 10 hours is 15·6 days. The time of repair after intestinal bleeding in Schiodt's observations in man was 33 days and in simple anaemia with optimal treatment (Gram, 1936) 33–40 days as compared with the 42 days we have calculated from the average reticulocyte count (0·7 per cent.) and maturation time (seven hours).

Various mechanisms of blood destruction have been assumed hypothetically by authors who have tried to estimate the duration of life of the erythrocyte by determining the time of recovery from experimental plethora. Boycott and Douglas (1909a) in three experiments found that rabbits' blood transfused into rabbits disappeared at an average daily rate of 0·441 c.c. oxygen capacity. 'This perhaps represents the rate of normal decay, and consequently of normal regeneration, the average "life" of a red cell being about 25 days.' This involves the assumption that the absolute figure for haemoglobin wastage remains unchanged in experimental plethora while the haemoglobin intake ceases. Escobar and Baldwin (1933) on the other hand produced experimental plethora in rabbits by exposure to low oxygen pressure for two to fourteen days and considered the time necessary to dispose of the excess of R.B.C. after return to atmospheric pressure as identical with the longevity of erythrocytes (eventually they added one half of the number of days constituting the period of low oxygen pressure). Here the assumption is either that the regeneration remains unchanged while the destruction increases in proportion to the highest degree of polycythaemia produced and that the destruction of R.B.C. is

determined by their age, or that the destruction is proportional to the density of the erythrocyte population present at any time of the experiment and that the longevity of red cells therefore changes with the decrease in the number of erythrocytes. In the first case the decrease would be linear: in the second a parabolic one (cf. Schiødt, 1938b). Actually Escobar and Baldwin found a linear decrease after short exposure to low oxygen pressure and after long exposure a rapid drop in the first three days followed by a slower fall. Many papers have been published on the subject of blood changes due to low oxygen pressure. Most of these investigations were not carried out with the aim of determining the life span of R.B.C. and in none of the papers are figures for reticulocytes given after return to atmospheric pressure. In the experiments of Krumbhaar and Chanutin (1922) on plethora after transfusion the destruction was certainly increased more than was proportional to the increase in total circulating haemoglobin as can be concluded from the figures for urobilin excretion; moreover experiments on plethora after transfusion are complicated by the occurrence of 'plethoric anaemia' (O. Robertson, 1917; Krumbhaar and Chanutin, 1922; Tyler and Baldwin, 1934) and the possibility of development of isohaemolysins such as have been demonstrated by Kambe and Komiga (1929) and O. Robertson (1917). Krumbhaar and Chanutin were unable to demonstrate agglutinins and haemolysins but their presence may well be suspected from 'the widespread evidence of agglutination and thrombosis' in post-mortem findings.

Spontaneous anaemia and spontaneous reticulocyte peaks

Experiments on phenylhydrazine anaemia in rabbits and guinea pigs afforded an opportunity to check the brilliant idea of Eaton and Damren (1930a and b) who started from the following consideration: If many red cells are removed at one time and are quickly replaced by new-formed cells, these will all die at about the same time, supposing that the death of erythrocytes is determined by their age, and will provoke a new reticulocyte response. They did indeed find a second peak in the reticulocyte curve eight days after the first in rabbits made anaemic by bleeding and they therefore consider eight days as the life span of rabbit's R.B.C. Unfortunately their experiments were carried out on two animals only and they only give percentage figures for reticulocytes without figures for the number of erythrocytes. It is therefore impossible to decide whether the peaks were due to real or only apparent increase in regeneration. Similar experiments were made independently by Schulten (1930) on rabbits, albino rats and albino mice. These show a spontaneous drop in the R.B.C. count about fifteen days after the onset of acute anaemia due either to phenylhydrazine or bleeding. Similar spontaneous falls in R.B.C. can be detected in charts reproduced by Ritz (1909), Isaacs (1924, chart 2), Inagaki (Schulten, 1930), and Istomanowa (1926), though they have escaped the attention of these authors.

In charts I–VI, figures for haemoglobin in gm. per cent. and for reticulocytes in ten thousands per c.mm. for four rabbits and two guinea pigs are graphically represented.* The reticulocyte curves show not only high peaks but also a series of smaller peaks the significance of which appears dubious. There are, however, several distinct peaks between which the reticulocyte counts show but little variation. Such peaks were seen in rabbit 15 on 3 Oct., and on 25 Oct., 1940; in rabbit no. 17 on 7 Aug. and 23 Aug. and on 6 Sept.; in rabbit no. 18 on 7 and 24 Aug., on 16 Sept., on 6 and 18 Oct., and in rabbit no. 20 on the 27 Sept. and 16 Oct. The time intervals are 22, 16, 14, 17, 23, 20, 12 and 19 days respectively, the average being 17·9 days. It is not perfectly correct, however, to take the time between two reticulocyte peaks as corresponding to the life span of R.B.C., rather is it the time between a reticulocyte peak when many new erythrocytes have entered the circulation and the next drop in R.B.C. and haemoglobin. Such 'spontaneous falls' have been observed more or less distinctly in all four rabbits occurring either on the same day as the reticulocyte response or preceding it by two to seven days. If this correction be taken into account the time intervals are 17, 17, 17, 16, 16, 10 and 16 days respectively with an average of 15·6 days. These times are in good agreement with that between the first and second fall of haemoglobin in the experiments of Schulten (1930) and are identical with the figure calculated from the maturation experiments. It is impossible to explain the difference from the results of Eaton and Damren (1930a and b) who found a time interval of eight days between two peaks. The assumption that their animals had erythrocytes of shorter longevity due to racial or environmental differences is not acceptable, for the pre-experimental reticulocyte count in their animals was rather lower than in the present series. It must, however, be realized that the figures here given do not represent the red cell's longevity for perfectly normal rabbits, for most hutch rabbits suffer to some extent from cage anaemia.

It is hardly possible to explain the findings of Eaton and Damren and of Schulten, which in their essence have been confirmed by the present experiments, in any other way than has been done by these authors. There are, however, some minor findings which can be explained only with the help of auxiliary hypotheses. Firstly if the cause assumed for spontaneous anaemia and secondary reticulocyte responses is correct there should be a considerable reduction in the destruction of R.B.C. in the period between the reticulocyte peak and the next fall in haemoglobin, but this is not the case, as may be seen from tables 1 to 4 and also in charts I to IV, which show that during periods of approximately constant

* When erythrocyte counts were not done, the calculation has been made on the basis of the colour index in one of the next counts. The colour index increases somewhat in phenylhydrazine anaemia but then remains unchanged for a long time.

haemoglobin level the reticulocyte concentrations were within normal limits. The second point arises from the two extremely severe spontaneous falls of haemoglobin observed in rabbits 17 and 18 between 55 and 60 days after the last phenylhydrazine injection.

It would certainly be incorrect to disregard the smaller falls of haemoglobin and reticulocyte peaks occurring during this period of 55 to 60 days, for a drop in haemoglobin of the same magnitude was seen in rabbit 15 twenty-two days after the last phenylhydrazine injection. The following consideration may explain these findings: Rous and Robertson (1917a and b) have shown that, in experimental anaemia brought about by bleeding, large numbers of corpuscles of soft, jelly-like consistence appear in the circulation, many of them soon breaking down into fragments. These fragments tend to accumulate in the spleen but may be encountered elsewhere as well. They stress the fact that in anaemia following haemorrhage 'the marrow must not only make up an initial blood lack, but while doing so must repair constant fresh losses due to the poor quality of cells put forth.' It appears probable that such erythrocytes of inferior quality are also formed in phenylhydrazine anaemia and the finding of increased destruction during recovery is consistent with this assumption. These erythrocytes are apparently destroyed indiscriminately, only some R.B.C. surviving a normal length of time. Variations in the percentage of such R.B.C. would explain not only the irregular, wave-like course of the reticulocyte count without definite peaks in the first experimental period of rabbit 15 but also the conspicuously severe falls in haemoglobin and reticulocyte responses in later periods.

The findings in guinea pig 21 differ quantitatively only from those in rabbits. The first reticulocyte peak is followed by a drop in haemoglobin between fourteen and twenty-one days later which results in a new reticulocyte peak. Fourteen days after this peak a new fall in haemoglobin starts lasting fifteen days. The time interval between the first and the second reticulocyte peaks is twenty-one days, and that between the second and third twenty-nine days. If the interval between the reticulocyte peaks and the mid point of the haemoglobin fall is taken into account the figures are 17·5 and 21 days. The average of twenty-five reticulocyte counts in seven normal guinea pigs was 2·02 per cent. which with a maturation time of 8 hours gives 16·6 days as an average life span for R.B.C. of guinea pigs.

In guinea pig 22 the destruction of R.B.C. by phenylhydrazine is followed by a slow recovery interrupted by several falls in the haemoglobin level. Only one of these is followed by a marked rise in the reticulocyte concentration. Thus though the phenylhydrazine injections caused a fall of haemoglobin of the same magnitude in this animal as in guinea pig 21 and a higher reticulocyte response the corresponding periods when numerous R.B.C. may be expected to die and to be replaced by new ones are not evident. Though only one out of six animals behaved in this way the finding is instructive for it indicates that senescence is not the only cause of death of erythrocytes. Observations on the other animals which did not show any reduction of the destruction between two reticulocyte peaks suggested that in all experiments some red cells did succumb as the result of other factors than old age. This may in part be due to the inferior quality in the cells and partly to a hypothetical ability of the organism to destroy red cells in proportion to its need for the derivatives of haemoglobin.

Further evidence of pathological conditions with indiscriminate destruction of R.B.C. will be given in the next article (part XIV).

Summarizing this part of the investigations it can be said that the findings of Eaton and Damren (1930a and b) and Schulten (1930) concerning the development of spontaneous anaemia and repeated reticulocyte peaks after a sudden loss of R.B.C. have been confirmed. The time intervals were different from those observed by the first two authors but

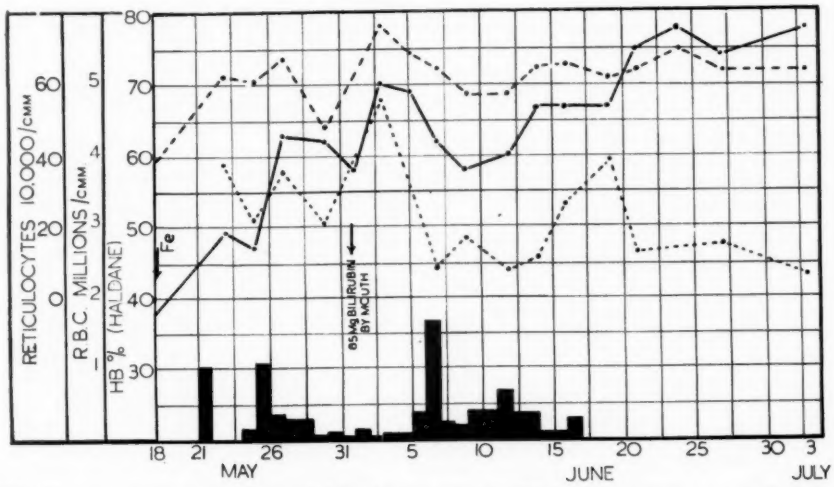

CHART XX.—Judith T. ———— Haemoglobin in per cent. (Haldane). – – – – – R.B.C. in millions per c.mm. – – – – –Reticulocytes in 10,000 per c.mm. The black columns represent the stercobilin excretion. The distance between two lines corresponds to 25 mgm. stercobilin.

were in good agreement with those of Schulten. The life time of R.B.C. concluded from the time interval between a reticulocyte peak and the next fall of haemoglobin is practically identical with that calculated from the number of reticulocytes and their maturation time as determined in vitro. The occurrence of repeated peaks shows that erythrocytes die mainly as the result of old age. Other findings, however, indicate that to some extent in all animals and particularly in one destruction of R.B.C. took place independently of their age.

Owing to the complicated conditions in erythronoclastic anaemia in man and even in pathological bleeding secondary falls in the number of R.B.C. and definite secondary reticulocyte peaks are not often met. They have occasionally been observed in pernicious anaemia after liver treatment. It must again be pointed out that conclusions as to the longevity of the red cell drawn from observations of the distance between two such peaks apply only to that particular disease, and that a certain amount of destruction of red cells may occur without reference to their age.

One case in which two definite reticulocyte peaks and two peaks in stercobilin excretion were observed is described below.

A girl, 10 months old, was admitted on May 15, 1939 to the Children's Hospital, Birmingham, under the care of Professor L. G. Parsons, suffering from severe hypochromic anaemia. As reticulocyte counts were not done on admission and stercobilin determinations were begun only after the start of iron treatment a definite classification of this anaemia is not possible. It is likely, however, that it was an iron deficiency anaemia complicated by a haemolytic process. The haemoglobin figures, the erythrocyte and reticulocyte counts, and the stercobilin excretion are shown in chart XX. The figures for stercobilin have here only a relative value as the fluoroscopic method of Elman and McMaster (1925) was used for their estimation and this method is standardized on an impure compound which is not crystalline. Bilirubin was determined by the method of Malloy and Evelyn (1938) over the same period.

The treatment with iron resulted in a rise of haemoglobin, R.B.C. and reticulocytes, a recovery which may be partly also due to the oral administration of 85 mgm. bilirubin. This rise was immediately followed by a fall and sixteen days after the first reticulocyte peak a second one occurs associated also with an increase in haemoglobin and to a less degree of R.B.C. Only 14 of the 85 mgm. of bilirubin were recovered in the stools, the whole of this within 24 hours of its administration. This was the only occasion on which bilirubin was found in the stools of this child. The figure is not shown in chart XX where the columns represent only figures for stercobilin. One week later a sudden rise in the stercobilin excretion occurred which can hardly be directly connected with the bile pigment given by mouth. The peaks in the stercobilin excretion are separated by a time interval of 12–16 days. (Unfortunately the stercobilin was not estimated on two days in the initial period). This time interval is in fairly good agreement with that between the reticulocyte peaks. If this time interval is compared with the life span of R.B.C. calculated from the number of reticulocytes and their maturation time the period between 22.6 and 3.7 only can be taken in account in which R.B.C., haemoglobin and reticulocyte levels were approximately constant. The average reticulocyte count in this period was 2·3 per cent. and the maturation time determined in vitro was 9·5 hours. The resulting regeneration rate $\left(\frac{2{\cdot}3 \times 24}{9{\cdot}5}\right)$ is 5·8 per cent. and since the level of R.B.C. and haemoglobin was constant the destruction rate must have been identical. The life span of R.B.C. therefore was 17·3 days. This agrees fairly well with the distance between the two reticulocyte and stercobilin peaks.

From a point of view similar to Eaton and Damren and Schulten but with a different experimental technique Hawkins and Whipple (1938) have recently performed experiments with the object of determining the life span of dog's erythrocytes. The amount of bile pigment secreted by bile fistula dogs was determined over a long period. The dogs were made anaemic by bleeding or by acetyl phenylhydrazine. The time interval between the midpoint of the most active haemoglobin regeneration and the following peak in bile pigment excretion was considered to correspond to the duration of life of the erythrocytes formed within the short period after experimental anaemia. This time interval was 113–133 days! The difference between this result and those of Eaton and Damren, Schulten and the present figures is so enormous that it can scarcely be explained by the use of different animals. It must be realized that the dogs of Hawkins and Whipple were not normal dogs but had bile fistulae which prevented the return of bile to the intestine. The authors say: 'If these dogs were slightly abnormal because of the bile fistulas the life cycle of the red cell presumably would be if anything slightly shorter than in the absolutely normal non-fistula dog.' Notwithstanding the brilliant work of Whipple and his school this point of view cannot be accepted. Work has already been mentioned which indicates that bile pigment is a stimulant to blood formation and the experiments of Kocvar and Ivy (1938) and of Schmidt, Beazel, Berman, Ivy and Atkinson (1939) show that the output of bile pigment when the bile is returned to the intestine is two or more times that when it is diverted. The difference can certainly not be explained by the 'enterohepatic circulation' of bile pigments for these are resorbed only in small amounts but is rather due to a stimulating action of bile pigments on the haemoglobin metabolism. Feeding of bile as in Hawkins and Whipple's experiments prevents the development of a bile fistula-anaemia but can apparently not replace the normal stimulus. It can be well imagined that with some substances supplied with the bile of food there is less need for blood destruction than in normal animals. The lower amounts of bile pigment secreted by bile fistula dogs in whom bile is prevented from returning to the intestine indicate a lower destruction and, with constant

haemoglobin level, a longer duration of life of the R.B.C. The figures of Hawkins and Whipple suggest that in their experiments the recovery from anaemia was rather due to reduction in the blood destruction than to increased regeneration; this suggests that the life span of erythrocytes was still further prolonged in the period following the experimental anaemia. This behaviour of bile fistula dogs shows a remarkable contrast to the experimental anaemia reported above where the initial stage of recovery was associated with a considerably increased blood destruction.

Summary

1. The regeneration of haemoglobin and the time of repair are studied in phenylhydrazine anaemia, post-haemorrhagic anaemia and 'spontaneous anaemia.'

2. The time of repair is not identical with the duration of life of erythrocytes. It does not represent the regeneration time but is the result of considerably increased regeneration and less considerably increased destruction.

3. The real regeneration in haemolytic anaemia, post-haemorrhagic and 'spontaneous' anaemia follows the kinetics of autocatalyzed reversible reactions. It is determined exclusively by the velocity of nuclear synthesis in the precursors of the red cells.

4. A decrease in the rate of destruction of red cells occurs only in the later stages of repair and only for short periods of time.

5. The majority of erythrocytes formed at one time die at the same time; some may be destroyed without regard to their age but old age is the main factor which determines the life span of erythrocytes.

(References are given at end of Part XIV).

RHEUMATIC INFECTION IN CHILDHOOD

BY

EDWARD C. ROSS COUPER, M.D., F.R.F.P.S., D.P.H.

Deputy Medical Superintendent, Walton Hospital, Liverpool; late Deputy Medical Superintendent, Alder Hey Children's Hospital, Liverpool

There are so many writings on the subject of rheumatic infection in childhood that it is with hesitation that another is added to the list. Yet in Alder Hey Children's Hospital, with the 950 beds available before the war and the large amount of clinical material, the possible scope of a survey seemed to justify an attempt to assess the problem as it affects a proportion of the child population of the City of Liverpool. It is not proposed to deal with the question of treatment in any detail and only a short statement will be made on this aspect.

Accommodation. Two wards of 30 beds each were set aside for the treatment of rheumatic infection and all children with this infection were admitted to these wards, which were kept as quiet as possible. Frequently the accommodation proved inadequate and many patients found their way into the general medical wards.

Routine. For the first six weeks the patient was kept flat with one pillow and no exertion was allowed. During this time the patient was fed by the nursing staff. At the end of six weeks the patient was allowed to feed himself sitting up for fifteen minutes. This period of fifteen minutes was gradually increased by fifteen minutes daily. When the patient got up he was allowed to sit for fifteen minutes in a chair, this period being increased by fifteen minutes daily, until he was up for two hours, after which the periods were increased by thirty minutes. Temperature, sleeping pulse and exercise pulse were accurately charted. On discharge the parents were requested to bring the child to the Rheumatism Clinic, which was purely an after-care clinic. From there children with badly damaged hearts were recommended to schools for physically defective children or referred to the care of the school medical officers.

Classification. In all 1796 cases, admitted during the years 1936, 1937 and 1938, were reviewed. Of these 164, 88 classified as rheumatism and 76 classified as chorea, were discarded as being too doubtful for inclusion in the series. As the patients were admitted at different stages in their illness, some in their first attack and some in the course of a subsequent attack, the basis upon which they have been classified is the condition of the child on admission to hospital. The conventional division into acute and subacute cases has not been employed as this is considered to be somewhat artificial and therefore often inaccurate. The 'rheumatism' cases could be divided most conveniently into two main groups, those presenting the classical features of acute articular rheumatism, with swelling, redness, etc., of joints (A.A.Rh.) and those presenting the syndrome of vague pains, 'growing pains,' anorexia, loss of weight and lassitude (V.P.). The cases of chorea were divided into mild, moderate and severe. Thus four main groups have been used in both diseases as follows:

A. RHEUMATISM. Those suffering on admission from—

(1) Acute articular rheumatism without heart involvement.
(2) Acute articular rheumatism with heart involvement.
(3) Vague pains with heart involvement.
(4) Vague pains without heart involvement.

B. CHOREA. Those suffering on admission from—

(1) Moderate chorea without heart involvement.
(2) Moderate chorea with heart involvement.
(3) Mild chorea with heart involvement.
(4) Mild chorea without heart involvement.

A relatively small number of cases of chorea were labelled 'severe,' i.e. they required the exhibition of sedatives for their control. To avoid the system of classification becoming too cumbersome these have been included in the 'moderate' groups and extracted later. The above eight groups have been further subdivided into (a) those who attended the after-care clinic; and (b) those who did not attend.

Results

TABLE 1

GENERAL ANALYSIS INTO THE GROUPS OF THE CLASSIFICATION

	A. Rheumatism			B. Chorea		
Group	(a)	(b)	Total	(a)	(b)	Total
1	63	54	117	139	100	239
2	71	60	131	81	67	148
3	233	221	454	53	35	88
4	145	95	240	115	100	215
Total	512	430	942	388	302	690

TABLE 2

ATTENDANCES AT AFTER-CARE CLINIC AND NUMBERS REFERRED TO PHYSICALLY DEFECTIVE SCHOOLS AND SCHOOL MEDICAL OFFICERS

	Attendances								P.D.S.	S.M.O.
	1	2	3	4	5	6	7	8		
RHEUMATISM 512 cases										
Number ..	88	82	57	18	8	7	5	2	41	80
Percentage ..	17·1	16·0	11·1	3·5	1·5	1·3	0·9	0·3	8·0	15·6
CHOREA 358 cases										
Number ..	76	73	42	18	10	10	1	2	8	54
Percentage ..	19·5	18·8	10·8	4·6	2·5	2·5	0·2	0·5	2·0	13·9

TABLE 3

SEX INCIDENCE

	Male	Female	Total	Ratio of M. to F.
Rheumatism	450	492	942	1 : 1·09
Chorea	207	483	690	1 : 2·3

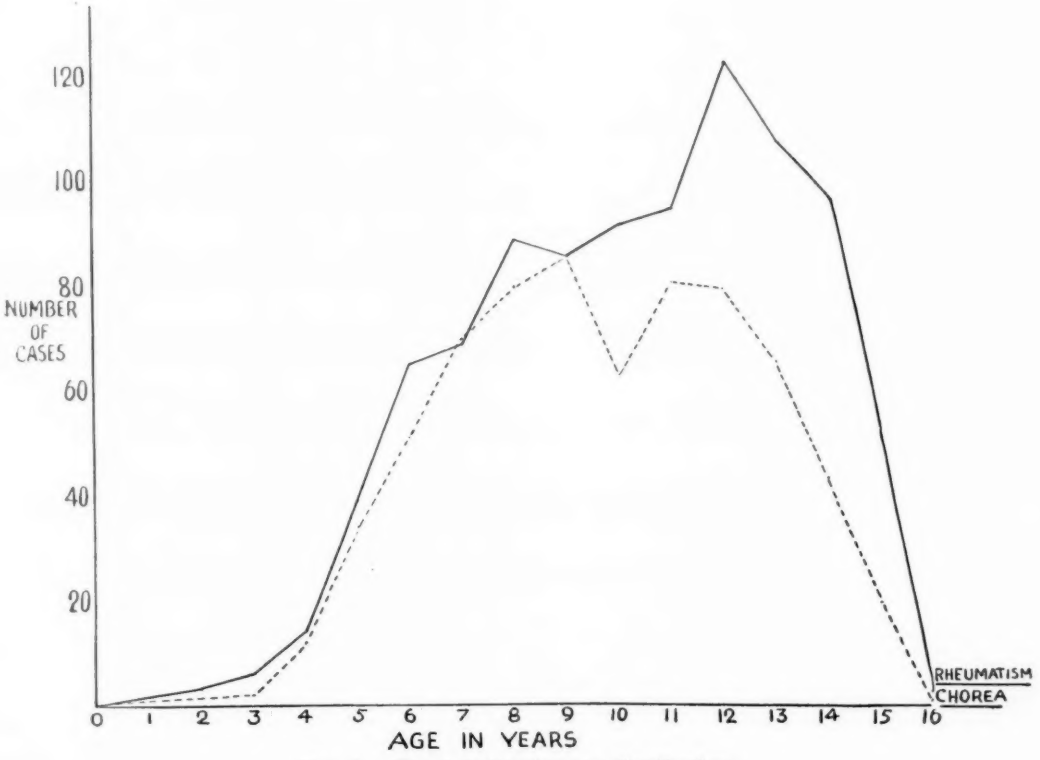

FIG. 1.—Graph indicating age distribution.

TABLE 4

A. RHEUMATISM—ANALYSIS OF CASES ADMITTED WITHOUT HEART INVOLVEMENT

Group A	No lesion	Mitral systolic which disappeared	Permanent mitral systolic	M.R.	M.R. and S.	M.R. and S. A.R.	M.R. and S. A.R. and S.	M.R. and A.R.	A.R.	Weight			Nodules	Erythema marginatum	History of tonsillitis	No. having 2nd attack	Lesion at 2nd attack	Death	Total
										Gain	Stationary	Loss							
1. A.A. Rh. without heart lesion—																			
(a) ..	32	11	5	12	2	—	1	—	—	26	13	7	1	1	27	10	3	—	63
(b) ..	24	8	3	13	1	1	1	2	1	—	—	—	3	1	17	7	4	2	54
4. V.P. without heart lesion—																			
(a) ..	90	33	1	14	5	—	1	—	1	73	20	24	3	2	59	38	6	—	145
(b) ..	57	12	4	22	—	—	—	—	—	—	—	—	—	2	29	6	2	1	95
Totals..	203	64	13	61	8	1	3	2	2	—	—	—	7	6	132	61	15	3	357
Percentages	56·8	17·9	3·6	17·0	2·2	0·2	0·8	0·5	0·5	—	—	—	1·9	1·6	36·9	17·0	4·2	0·8	—

M.R. = Mitral Regurgitation. M.R. and S. = Mitral Regurgitation and Stenosis. A.R. = Aortic Regurgitation. A.R. and S. = Aortic Regurgitation and Stenosis.

TABLE 5

A. RHEUMATISM—ANALYSIS OF CASES ADMITTED WITH HEART INVOLVEMENT

A. RHEUMATISM Groups 2 and 3		A 2 (a)	A 3 (a)	A 2 (b)	A 3 (b)	Totals	Percentages
Lesions on admission which remained unaltered except in (1)	(1) Mitral systolic which cleared	20	68	15	28	131	22·3
	(2) Mitral systolic→permanent	2	7	—	11	20	3·4
	(3) M.R.	14	54	11	47	126	21·5
	(4) M.R. and S.	4	33	8	58	103	17·6
	(5) M.R. and A.R.	2	3	—	—	5	0·8
	(6) M.R. and S., and A.R. ..	—	2	1	7	10	1·7
	(7) A.S.	1	—	—	—	1	0·1
	(8) M.R. and S., A.R. and S. ..	—	—	—	3	3	0·5
Lesions which progressed while in hospital	(1) M.R.→M.S.	8	22	9	24	63	10·7
	(2) M.R.→A.R.	4	3	1	2	10	1·7
	(3) M.R.→M.S.→A.R.	—	—	1	11	12	2·0
	(4) M.R. (becoming well established) ..	15	35	11	22	83	14·2
	(5) M.R. and S.→A.R. and S.	1	2	—	3	6	1·0
	(6) A.R.→A.R. and S. (W.R. negative) ..	—	1	—	—	1	0·1
	(7) M.R. and S.→A.R.	—	2	1	7	10	1·7
	(8) M.R.→M.R. and S. and A.R. and S.	—	—	—	1	1	0·1
Weight	Gain	43	146	—	—	189	—
	Stationary	9	20	—	—	29	—
	Loss	9	24	—	—	33	—
	Nodules	9	25	3	35	72	12·3
	Erythema marginatum	1	4	1	5	11	1·8
	History of tonsillitis	23	83	18	45	169	28·8
	Number having second attack	18	79	16	84	197	33·6
	Number developing lesions second attack	10	24	6	28	68	11·6
Pericarditis	Total	4	19	8	31	62	10·5
	Number which cleared	4	19	5	10	38	6·4
	Number developing while in hospital ..	3	5	8	18	34	5·8
	Number on admission	1	14	—	13	28	4·7
	Died	—	—	3	21	24	4·1
Pericardial	Adhesions (old)	1	8	—	10	19	3·2
Cardiac failure	Total	—	6	—	35	41	7·0
	Number developing while in hospital ..	—	1	—	10	11	1·8
	Number on admission	—	5	—	25	30	5·1
	Died	—	2	—	24	26	4·4
Auricular fibrillation		—	2	—	2	4	0·6
Malignant endocarditis		—	—	1	1	2	0·3
Total deaths		—	2	4	48	54	9·2

TABLE 6

B. CHOREA—ANALYSIS OF CASES ADMITTED WITHOUT HEART INVOLVEMENT

Group B	No lesion	Mitral systolic which disappeared	Permanent mitral systolic	M.R.	M.R. and S.	M.R. and S. and A.R.	Weight			Tonsillitis	Number having previous attacks		Lesion at 2nd attack	Total
							Gain	Stationary	Loss		Ch.	Rh.		
1. Ch. (a) Moderate	75	21	2	16	—	—	57	11	14	19	33	5	10	114
Severe ..	16	6	1	1	1	—	15	0	3	5	6	3	1	25
(b) Moderate ..	65	3	1	23	1	—	—	—	—	8	20	8	9	93
Severe ..	4	—	—	2	1	—	—	—	—	1	3	2	2	7
4. Ch. (a) Mild ..	93	14	2	6	—	—	50	16	10	14	19	8	3	115
(b) Mild	82	7	1	8	2	—	—	—	—	16	30	6	5	100
Totals ..	335	51	7	56	5	—	—	—	—	63	111	32	30	454
Percentages	73·5	11·2	1·5	12·3	1·1	—	—	—	—	13·8	24·4	7·0	6·6	—

TABLE 7

B. CHOREA—ANALYSIS OF CASES ADMITTED WITH HEART INVOLVEMENT

B. CHOREA Groups 2 and 3		B 2 (a)	B 2 (b)	B 3 (a)	B 3 (b)	Totals	Percentage
MODERATE Lesions on admission, which remained unaltered except in (1)	(1) Mitral systolic which cleared ..	21	14	18	11	64	27·1
	(2) Mitral systolic→permanent ..	6	4	5	4	19	8·0
	(3) M.R.	21	26	14	5	66	27·9
	(4) M.R. and S.	3	1	3	3	10	4·2
	(5) M.R. and S., A.R. and S. ..	—	1	—	—	1	0·4
Lesions which progressed while in hospital	(1) M.R.→M.S.	7	6	2	3	18	7·6
	(2) M.B.→A.R.	—	—	1	—	1	0·4
	(3) M.R.→M.S.→A.R.	—	1	—	—	1	0·4
	(4) M.R. (becoming well established)	19	9	12	7	47	19·9
Weight	Gain	50	—	25	—	75	55·9
	Stationary	9	—	9	—	18	13·4
	Loss	7	—	4	—	11	8·2
History of tonsillitis		10	10	9	1	30	12·7
Number having second attack of chorea		21	23	16	15	75	31·7
History of rheumatism		11	9	5	1	26	11·0
Number developing lesions at second attack		12	3	4	5	24	10·1
SEVERE Unaltered lesions, except in (1)	(1) Mitral systolic which cleared ..	2	—	—	—	2	0·8
	(2) Mitral systolic→permanent ..	1	—	—	—	1	0·4
	(3) M.R.	2	1	—	—	3	1·2
Progressing lesions	M.R. becoming well established ..	1	3	—	—	4	1·6
	M.R.→M.R. and S.	1	—	—	—	1	0·4
	M.R. and S.→A.R. and S. ..	—	1	—	—	1	0·4
Congestive cardiac failure developing in hospital		—	2	—	—	2	0·8
Death		—	3	—	—	3	1·2

In addition to the foregoing detailed tables, it has been possible to obtain the following information:

Relapse rate. During the period under review, i.e. 1936, 1937, 1938, cases re-admitted have not been included twice, but note of their re-admission taken. From these figures the relapse rate can be calculated approximately:

RHEUMATISM. 66, of whom 7 died at subsequent admission.

Therefore relapse rate = 7·0 per cent.

CHOREA. 75.

Therefore relapse rate = 10·7 per cent.

Prognosis. Of the 1632 cases, 49 were recommended to attend schools for physically defective children. This figure is probably somewhat smaller than it should have been, as, owing to lack of accommodation, such recommendations were reduced to a minimum. 134 children were referred to the School Medical Officer for further observation:

i.e. 1389 (85·1 per cent.) may be said to be in good health
183 (11·2 per cent.) may be said to be in poor health
60 (3·6 per cent.) have died.

Clinical type. Of the 942 cases of rheumatism 245 (26·3 per cent.) were of the A.A.Rh. Group and 694 (73·6 per cent.) were of the V.P. Group, i.e. the syndrome of vague pains, 'growing pains,' lassitude, etc., is about three times as common as the acute articular type.

In the chorea group (group B) there were in all 690 cases, of whom—

45 (6·5 per cent.) were severe,
342 (49·5 per cent.) were moderate,
303 (43·9 per cent.) were mild.

Of the mild chorea, 16 out of 215 (7·4 per cent.) developed lesions de novo.

Of the severe chorea, 5 out of 32 (15·6 per cent.) developed lesions de novo.

Incidence of heart lesions and attacks

RHEUMATISM. Of the 942 cases, 684 were having their first attack and 258 were having their second or subsequent attack.

Of the 684 (first attack) cases, 180 (26·3 per cent.) developed lesions or progressed.

Of the 258 (second attack) cases, 83 (32·1 per cent.) developed lesions or progressed.

CHOREA. Of the 690 cases, 504 were having their first attack and 186 were having their second or subsequent attack.

Of the 504 (first attack) cases, 134 (26·5 per cent.) developed lesions or progressed.

Of the 186 (second attack) cases, 54 (29·0 per cent.) developed lesions or progressed.

Incidence of the various heart lesions or combinations of heart lesions—final result.

(a) Mitral regurgitation	446
(b) Mitral regurgitation and stenosis	208
(c) Mitral regurgitation and stenosis and aortic regurgitation	34
(d) Mitral regurgitation and stenosis and aortic regurgitation and stenosis	15
(e) Mitral regurgitation and aortic regurgitation	18
(f) Aortic regurgitation and stenosis	1
(g) Aortic regurgitation	2
(h) Aortic stenosis	1

Removal from hospital. Of the 1632 cases, 119 (7·2 per cent.) were taken home on their parents' responsibility, one of them on two occasions.

Death rates

(a) General death rate—of 1632 cases, 60 (3·6 per cent.) died.

TABLE 8

SHOWING INCIDENCE OF HEART INVOLVEMENT

	Rheumatism	Average per annum	Chorea	Average per annum	Total	Average per annum
'New Hearts'	77	25	61	20	138	46
Established 'Hearts' treated	248	82	80	28	328	109
Established 'Hearts' which progressed	186	62	73	24	259	86
Total	511	170	214	71	725	241
Percentage	54·2		31·0		44·4	
No lesion	203	67	335	111	538	179
Mitral systolic which disappeared	195	65	115	38	310	103
Doubtful	33	11	26	8	59	19

Incidence of heart lesions in clinical types

RHEUMATISM (Group A, 1 and 4—presenting no lesion on admission).

Of the A.A.Rh. group, 34 out of 117 (29·0 per cent.) developed lesions de novo.

Of the V.P. group, 43 out of 240 (17·9 per cent.) developed lesions de novo.

CHOREA (Group B, 1 and 4—presenting no lesion on admission).

Of the moderate chorea, 40 out of 207 (19·3 per cent.) developed lesions de novo.

(b) Rheumatism death rate—of 942 cases, 57 (6·0 per cent.) died.

(c) Chorea death rate—of 690 cases, 3 (0·4 per cent.) died.

(d) Rheumatic cases which possessed or developed 'hearts,' death rate—of the 511 cases, 57 (11·1 per cent.) died.

(e) Choreic cases which possessed or developed 'hearts,' death rate—of the 214 cases, 3 (1·4 per cent.) died.

Incidence of transient systolic murmur

RHEUMATISM. Of the 585 cases with heart involvement on admission, 195 (33·3 per cent.) had a mitral systolic murmur which disappeared.

CHOREA. Of the 236 cases with heart involvement on admission, 115 (48·7 per cent.) had a mitral systolic murmur, which disappeared.

Total 821, 310 (37·7 per cent.).

TABLE 9

INCIDENCE OF TONSILLITIS

RHEUMATISM	Without history of tonsillitis 608 cases		With history of tonsillitis 301 cases	
	Number	Percentage	Number	Percentage
1. Lesions which developed or progressed ..	182	29·9	81	27·2
2. Lesions on admission which did not progress	208	34·2	40	13·2
3. No lesion	218	35·8	180	59·0
CHOREA	571 cases		93 cases	
	Number	Percentage	Number	Percentage
1. Lesions which developed or progressed ..	124	21·7	10	10·7
2. Lesions on admission which did not progress	68	11·9	12	12·9
3. No lesion	379	66·3	71	76·3

Pericarditis. One case occurred in the chorea group, which died.

In the rheumatism group there were 64, of whom 25 (39·0 per cent.) died.

In the A.A.Rh. group there was 1 case which recovered.

In the V.P. group there were 63 cases, of whom 25 died.

Congestive cardiac failure. There was a total of 43 cases, of whom 28 (65·1 per cent.) died.

Nodules

RHEUMATISM. (Group A, 1 and 2—A.A. Rh.). Of 248 cases, 16 (6·4 per cent.) had nodules.

(Group A, 3 and 4—V.P.)

Of 694 cases, 63 (9·0 per cent.) had nodules.

The sex distribution was approximately equal.

Of the 942 cases of rheumatism, 79 (8·2 per cent.) showed nodules.

Of the 79 cases with nodules, 19 (24·0 per cent.) died.

Of the 19 deaths, 12 (63·1 per cent.) occurred in association with pericarditis.

Erythema marginatum. Of the 942 cases of rheumatism, 17 (1·8 per cent.) showed erythema marginatum, and of these only one died in congestive cardiac failure.

Incidence of affection in various joints in A.A.Rh.

Ankles	210
Knees	117
Wrists	55
Hips	13
Elbows..	12
Fingers	8
Shoulders	3

Occasionally lesions of the hip-joint and more rarely the knee-joint, when such joint was the only one affected at the time of examination, gave rise to difficulty in diagnosis between rheumatic infection and osteomyelitis, or septic arthritis, especially when the child had a high temperature and looked ill. A useful diagnostic sign was observed in the presence or absence of delirium. In the presence of delirium the lesion was invariably found to be either osteomyelitis or septic arthritis. Delirium has not been observed in cases of rheumatic infection.

Temperature and pulse. For this purpose the group of acute articular rheumatisms admitted without evidence of heart involvement have been analysed (117 cases; unit of time = 3 days).

TABLE 10

Type of case	Temperature in units					Pulse in units						
	1	2	3	4	5+	1	2	3	4	5	6	7+
Heart lesion which developed or progressed	12	13	4	1	3	0	12	16	2	2	1	1
Cases developing a mitral systolic murmur which disappeared	16	7	1	0	0	3	10	14	1	0	0	0
No lesion	28	15	3	0	0	5	22	16	2	0	0	0

Discussion

It is not proposed to deal with the extensive literature on this subject in any detail and reference will only be made to a few of the larger surveys. Some justification for the classification employed may be found in a statement by Findlay (1931), who, dealing with the assessment of the incidence of rheumatic infection says, ' It would also be advisable that chorea and arthritis, with and without carditis, be also specifically stated, as it is only in this way that the personal bias of the individual medical man can be eliminated, and definite information regarding the relative frequency of the mild and grave types of the disease elicited.' Table 1 demonstrates

the well-known fact that the classical picture of acute articular rheumatism with swelling, redness and pain in joints is considerably less frequent than the syndrome of vague pains, 'growing pains,' lassitude, etc. The insidious nature of the infection is one of the most potent factors in rendering control of this disease extremely difficult. This has been the experience elsewhere, e.g. Ministry of Health Report, No. 44 (1927), in which it is stated that arthritic phenomena are not so common as vague symptoms. Considerably fewer cases of chorea were admitted with signs of heart involvement than was the case in rheumatism. The table also shows that, while the physician in charge of the after-care clinic considered that the clinic was at times busy, in fact, 44·8 per cent. did not attend at all, and table 2 shows that the record of those who did attend was not all that could be desired. Table 3 demonstrates once again the well-known higher incidence of chorea in girls, the ratio being males: females as 1: 2·3. Findlay's figure is 1: 2·8. He also finds arthritic phenomena commoner in girls, the ratio being 1: 1·1 and the ratio in the present series is almost identical—1: 1·09. The graph (fig. 1) indicates the age distribution. The terminal fall between the ages of 14 to 16 years may be to some extent artificial as cases over 16 were not admitted. Still, the graph is similar to that illustrating Schlesinger's Milroy Lectures (1938). Tables 4, 5, 6 and 7 show that valvular lesions occur in the following order of frequency—mitral regurgitation, mitral regurgitation and stenosis, and aortic disease. Without going into detail this is in accord with other writings, e.g. Findlay: mitral regurgitation 473, mitral stenosis 216, aortic regurgitation 59; and Schlesinger: mitral regurgitation 368, mitral stenosis 272, mitral and aortic disease 85. Aortic stenosis alone is extremely rare and was only noted in one case. Schlesinger (1938) mentions only two which were in combination with mitral disease.

The relapse rate (8·8 per cent.) has been calculated approximately, as nothing is known of those who probably relapsed, but did not report at the hospital. For this reason the present figure is lower than other recorded figures. Schlesinger found 35 per cent. in his series, whilst other authors put it as high as 60 to 70 per cent. Forrest Smith (Ministry of Health Report, 1927), who rightly calls attention to the difficulty in deciding what is and what is not a relapse in the course of such a prolonged disease, found a relapse rate of 85·3 per cent. In another series she mentions that 77 per cent. of cases were treated as out-patients from their homes, while all the cases in the present series had adequate hospital treatment. It is possible that herein lies one reason for the great discrepancy between her relapse rate and that of the present series.

The percentage of the cases who are alive and well (85·1 per cent.), is similar to the findings of Schlesinger (81·7 per cent.), but there are discrepancies between his figures of those in poor health and those who are dead, and the figures of the present series. These discrepancies will be dealt with later. 44·4 per cent. were found to develop heart lesions or to possess heart lesions. An average of 46 'new hearts' and an average of 86 heart lesions which progressed, occurred each year. These figures are rather lower than those found by Findlay, who states that heart disease occurs in 75 per cent. of rheumatic arthritis and in 50 per cent. of chorea. On the other hand they are worse than Forrest Smith's figures. In her first series 21·9 per cent. had heart lesions and in her second series 29·8 per cent. In the rheumatic group a materially greater percentage of heart lesions developed in the group of acute articular rheumatism than in the group presenting the 'vague pains syndrome.' In the moderate and severe choreas there is no great difference. There is a greater incidence of heart disease in rheumatism than in chorea, which is in agreement with Findlay's findings. 26·3 per cent. developed lesions or progressed during their first attack, while 32·1 per cent. did so during their second or subsequent attack. The difference is not so striking in the case of chorea. In general this is in accord with Findlay's findings. The general death rates are remarkably low, i.e. in rheumatism, only 6 per cent., which is lower than Schlesinger's figure of 12·3 per cent. It must be remembered that his series is composed of cases of rheumatic heart disease. In the present series, in those cases of rheumatism which developed or possessed heart lesions, the death rate is 11·1 per cent., which is similar to Schlesinger's figure.

It is suggested that, as all cases of rheumatic infection are included in the present series, the death rate of 6 per cent. gives a more accurate idea of the death rate in this infection. In 37·7 per cent. of the cases a mitral systolic murmur disappeared. Similar figures have been found by various authors. Schlesinger quotes 30 per cent. by Carey Coombs and 37 per cent. by Morse. Findlay had 54 such cases, but found that in a proportion this murmur returned after a period of years. He suggests myocarditis as the cause of such murmurs. Forrest Smith had 21·3 per cent. of such cases in her first series and 23·5 per cent. in her second.

Most writers seem to agree that tonsillitis plays a part in the etiology of rheumatic infection, and many figures are produced to show that there is a greater incidence of tonsillitis and tonsillar infection in rheumatic subjects than in non-rheumatic subjects. As the prognosis in rheumatic infection depends upon whether the heart is affected or not, it is strange that the authors consulted have not tried to establish the relationship between tonsillitis and the occurrence of heart involvement. An attempt has been made to do this in the present series with a somewhat unexpected result. Table 9 shows that in those with a history of tonsillitis 27·2 per cent. had lesions which developed or progressed, while in those with no such history the percentage was 29·9 per cent. In chorea tonsillitis appears to exert no influence on the incidence of heart disease. Findlay found a history of tonsillitis

in only 4 per cent. of his cases and as he says, in the Medical Research Council's Report, No. 114 (1927), a history of recurrent sore throat was obtained in 18 per cent. of rheumatic cases and in 16 per cent. of non-rheumatic cases or control cases. In pericarditis the death rate of 39·0 per cent. compares favourably with other figures, e.g. Schlesinger 50 per cent. and Findlay 63·4 per cent. The presence of nodules is generally regarded as of bad omen, and this is confirmed in the present series. Their incidence is roughly similar to that discovered by Schlesinger (9 per cent.) and Findlay (10 per cent.). Schlesinger's death rate (40 per cent.) is rather higher than in the present series and a high percentage was found in association with pericarditis, both in the present series and by Findlay. Erythema marginatum was found in only a small proportion of cases. The incidence of affection of the various joints is parallel with Findlay's experience. He has found affection of the right hip-joint simulating appendicitis and leading to operation. The present writer has not experienced this complication. Temperature and pulse rates are not always helpful, although a greater number of cases with prolonged pyrexia and elevation of pulse rate is found in the cases which developed heart lesions. Pyrexia may be absent in active cases.

Comment

At the present time, when planning for the future bulks so largely on the medical horizon, the present series serves to re-emphasize the great importance of rheumatic infection in childhood. This is especially important when it is considered that diseases of the heart and circulation have the highest death rate and that 50 to 60 per cent. of these are due to rheumatic infection, a large proportion of which is acquired in childhood. An average of 241 cases per annum of rheumatic heart disease in one hospital is a startlingly large number. It has been estimated that the number of beds necessary for the adequate treatment of rheumatic infection in childhood should be computed on the basis of 1·7 beds per 1000 elementary school children. In the City of Liverpool the number of elemenary school children, taking 1937 as an average year, was 132,884, so that at least 225 beds should be available. Probably this is an inadequate figure. An attempt was made in Alder Hey Children's Hospital to treat all cases of rheumatic infection or suspected rheumatic infection, whether showing evidence of cardiac involvement or not. Findlay says, ' It cannot be too strongly stated that it is to the milder example of the disease and especially before the heart has been involved, that particular attention should be paid, since the greatest achievement of our treatment and the greatest blessing to the patient is to keep the heart from becoming affected.' In the opinion of the writer it is impossible, in the course of one or even two examinations as an out-patient, to determine whether the rheumatic process is active or not. It is necessary to have the child under close and skilled observation in bed in hospital for a period of a few weeks. If this ideal situation is to develop then perhaps an even greater number of beds should in the future be made available for this purpose.

It is generally agreed that rheumatic clinics or after-care clinics are extremely useful; but when the child is referred to the school medical officer, or to a school for physically defective children, he passes out of the care of the physician who knows the child from the inception of his illness. Whilst it is not intended to criticize adversely the admirable work of the school medical service, it is felt that arrangements should be made whereby the hospital physicians supervise the progress of the rheumatic child while at the school for physically defective children. In other words, there should be continuity of supervision. The ideal is the residential school such as is in operaton in Birmingham. In the writer's opinion such schools should be medically supervised by the physician of the hospital and preferably should be in adjacent premises if the parent hospital is suitably situated. Education in such schools should to a greater extent be designed to fit the cardiac cripple for some useful employment. The writer has frequently recommended a sedentary occupation, only to find that the child's educational attainments automatically debar him from such employment. It was disappointing to find that only 50 per cent. attended the after-care clinic and that those who did attend, attended so badly. The remedy lies in teaching parents the dangers of rheumatic infection, and eradication of the common idea that the function of a clinic is to supply a bottle of medicine.

On the whole the prognosis is not unfavourable and the writer is convinced that it could be improved by early and continuous supervision, if necessary until adolescence is reached. There is little justification for the view recently expressed by Parsons-Smith (1942) that ' in children carditis in some form is practically an inevitable development.' The problem is an immense one and in planning the medical service of the future it merits detailed consideration.

Thanks are due to Dr. W. E. Crosbie, Medical Superintendent, Alder Hey Children's Hospital, Liverpool, for permission to publish this paper; and to Dr. N. B. Capon for his advice and criticism.

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PLASMA PROTEIN VALUES IN INFANTS

BY

EVELYN M. HICKMANS, M.Sc., Ph.D., ETHEL FINCH, M.Sc., and EVA TONKS, M.Sc.

(From the Children's Hospital, Birmingham)

There are only a few reports in the literature dealing with the amount of plasma or serum protein during the neonatal period; nor is there agreement as to the normal amount of protein in children under one year of age. Several workers have stated that the serum of infants contains considerably less protein than that of adults and that there is a gradual increase in the concentration of the serum proteins throughout the first year of life, at the end of which time adult values are reached.

Ray and Phatak (1930) give a value of 7·0 gm. per 100 c.c. for total protein in new-born infants (twenty cases). According to Kylin (1932) the range of values for the serum protein of children under two years of age is 4·6 to 6·5 gm. per 100 c.c. Darrow and Cary (1933), using the Kjeldahl method, give a value of 4·9 gm. per 100 c.c. of serum for premature babies, 5·52 gm. per 100 c.c. for normal new-born babies and 6·29 gm. per 100 c.c. for children of five to eight months of age. Rennie (1935) gives a range of 6·04 to 8·0 gm. per 100 c.c. of serum for apparently normal children three to twenty-three months of age with an average of 7·08 gm. per 100 c.c. He states that 'the figures for infants over three months of age and for older children show little difference either in range or average.'

No doubt some of these differences have arisen owing to the use of different methods of estimation. For instance, it has been established that a refractometer method gives somewhat higher values than Kjeldahl estimations and this discrepancy between the two methods is increased if the plasma is lipaemic.

In this note the plasma protein values of a hundred and eighty normal full-term infants and young children and of twenty premature infants are reported. Many of these children were attending infant welfare centres. Those under two weeks of age were in a maternity hospital. Estimations were made by the micro-Kjeldahl method followed by Nesslerization. Only 0·01 c.c. of plasma was used which was obtained from a heel prick and collected over heparin in a micro-test-tube. The results of these estimations are recorded graphically, those for premature infants being separated from those of full-term infants. For comparative purposes some estimations were made on normal adults, the same method being used and the blood being collected from the lobe of the ear. These results are shown in a separate column.

From the figures thus obtained the following deductions can be drawn:

(1) In the first two weeks of life, the full-term

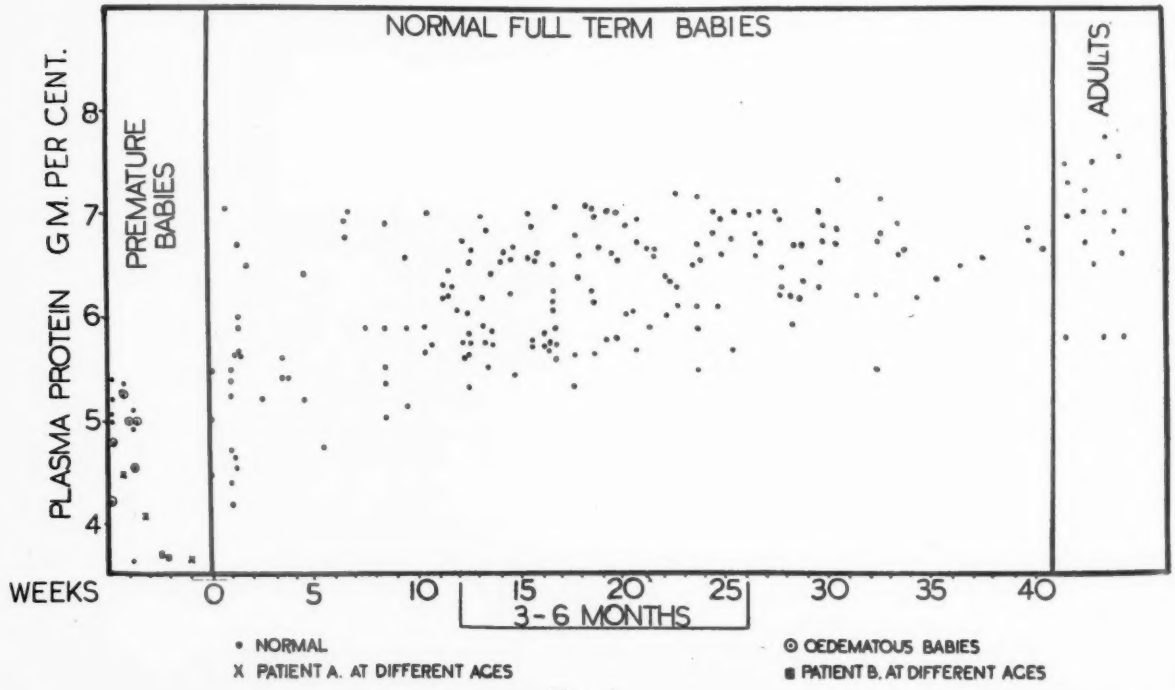

FIG. 1.

infant may have a plasma protein value of from 4 to 7 gm. per 100 c.c. In the majority of instances in this series the plasma protein is below 6 gm. per 100 c.c.

(2) The values for premature infants in the first four weeks of life are somewhat lower, and range from 3·7 to 5·4 gm. per 100 c.c. In two infants from whom blood was taken on several occasions, the value decreased.

(3) The range for full-term infants over two to three weeks old is from 4·7 to 7·4 gm. per 100 c.c.

(4) In infants over ten weeks of age, most of the values lie in the upper half of this range, viz. between 6 and 7·4 gm. per 100 c.c. The majority of the figures for adults recorded here also lie within this somewhat more limited range but sometimes reach higher figures than any observed in this series of infants.

It is interesting to note that McCarthy (1938) reports two observations on the total protein concentration in un-dialysed serum of two maternal sheep and their lambs. The figure obtained for lamb 2 was 4·89 per cent. and sheep 2 was 7·98 per cent. Another lamb serum had a protein concentration of 4·34 per cent. and the corresponding maternal serum contained 6·61 per cent. These findings have not yet been fully explained.

Summary

Premature infants particularly, and normal full-term infants up to two to three weeks of age show a lower plasma protein value than infants from three weeks of age to nearly one year. In infants over three weeks old, the values approach closely to those obtained from normal adults.

The expenses of this work have been partly defrayed by the Medical Research Council to whom thanks are due.

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CASE REPORTS

AN UNUSUAL OSSEOUS DYSTROPHY

BY

JAMES F. BRAILSFORD, M.D., Ph.D., F.R.C.P.

Honorary Radiologist, Royal Cripples Hospital, and Consulting Radiologist to City of Birmingham Hospitals

The patient, J. C., whose physical and radiographical features are described in this paper, is a girl aged thirteen years. She has been under clinical and radiographic observation at The Royal Cripples Hospital since she was five years of age. She was born of normal parents who are unrelated; pregnancy was normal. There were no miscarriages, and the only other child (a younger boy, now aged ten) is normal. For the first two years of life the patient was thought to be normal, but after this time an obvious deformity of the spine developed for which treatment was sought from the late Mr. Naughton Dunn and since from Mr. F. G. Allan. She now shows a remarkable degree of dwarfing. At the age of five she was but 25 in. in height; this increased to 27 in. at the age of seven and to 28 in. at the age of thirteen in 1942. She weighs 38 lb. As will be seen from the photograph (fig. 1) she appears to have a very short neck and a marked spinal curvature, a severe scoliosis of the lower dorsal spine associated with a marked lumbar lordosis and a bilateral coxa vara. Abduction of the legs and arms is restricted—the arms cannot be raised above the shoulders. The hands and feet are broad and stubby. The relative lengths of the limbs and trunk show no marked departure from the normal. There is no swelling of the peripheral joints and, apart from the limitations already indicated, movements of the limbs are free. She can run about and play with other children, but tires more quickly than they. She is a bright affectionate child and attends school with her brother. Owing to her repeated stays in hospital her education is backward, but her mother states that she is 'all there' and can be left with confidence in charge of the house and her brother, who is a boy of ten years of normal size and intellect (fig. 2). Her hair appears to be of normal sheen and coarseness.

FIG. 1.

FIG. 2.

There is no axillary or pubic hair, and no development of the breasts. No enlargement of the liver or spleen could be detected; the eyes appear to be clear and bright. The teeth are irregular and ill-developed and carious. In grotesque appearance she presents a superficial resemblance to the case of gargoylism (case 1, H. W., aged eighteen) described by Ellis, Sheldon and Capon (1936).

Radiographic examination

THE SKULL. No definite abnormality seen; all the sutures are shown. Normal sella. Sinuses are well developed. All the teeth have erupted except the wisdoms which can all be seen in the radiographs.

SPINE. The vertebrae are of mature shape; there is no indication of vascular channels, epiphyses or delay in fusion of the elements. The lower part, which includes all the vertebrae from the ninth dorsal to the lower sacral forms a marked forward and regular curvature which includes the lumbo-sacral curvature. The dorsal vertebrae from the fourth to the ninth form a very marked convexity backward and to the left (a kyphoscoliosis) the heart being pushed over to the right. The ribs on the right show a marked compensatory curvature. No abnormality can be detected in the form or curvature of the vertebrae above the fourth dorsal (fig. 3 and 4). The clavicles are slender but otherwise normal.

THE UPPER EXTREMITY. The scapulae because of the curvature are elevated; they show poor development of the glenoid fossae.

Humerus.—The capital epiphyses, developed from three somewhat irregular ossific nuclei which have been compressed, are flattened and devoid of the normal ball-like articu'ar surface. The shafts are somewhat shorter than normal. The epiphyses for the lower end were late in developing and have not fused at the age of thirteen years.

Ulna and radius.—The nucleus for the head of the radius did not appear until the age of ten years. It is of greater density than the normal epiphyses and has not yet fused. The lower radial epiphysis was present at the age of five, together with nuclei for the os magnum and unciform. At ten years nuclei for the trapezium and trapezoid had been added as well as a smaller one for the left cuneiform.

FIG. 3.

FIG. 4.

At thirteen, nuclei for the scaphoid and semilunar have appeared; these are still rounded and present no evidence of their normal characters.

Hand.—All the epiphyses for the metacarpals and phalanges were laid down in single dense nuclei. At the age of five all nuclei were distinguishable with the exception of the terminal phalanges, base of first and head of the fifth metacarpals. At seven years the nucleus for the head of the fifth had appeared. At ten years a minute nucleus for the base of the first was recognizable; the epiphyses for all the proximal phalanges of the left fingers and the right ring and little fingers had fused; some had lost their unusual density and were now of the density of the diaphyses (fig. 5). At thirteen years all the epiphyses of the metacarpals and phalanges had fused and most had lost the unusual density which had formerly been a noticeable feature. No sign was seen of any epiphyses for the terminal phalanges.

The foot.—The tarsus, metatarsus and phalanges showed similar delay and radiographic appearances to those seen in the bones of the hand except that dense epiphyses for the terminal phalanges were present at the age of five years. In the case of the little toes the dense epiphyses for the terminal phalanges up to the age of thirteen were the only ossific representation of these bones. The opposing bony surfaces of the tarsus and metatarsus during development presented an unusually sharp cut angularity.

Differential diagnosis

GARGOYLISM. Ellis, Sheldon and Capon (1936) gave this name to patients having the syndrome 'a peculiar type of osseous dystrophy, congenital clouding of the cornea, enlargement of the liver and spleen and mental deficiency.' They chose the name 'on account of the large head, grotesque, inhuman facies and deformed limbs which suggest the appearance of gargoyles and render the patients closely similar to one another and the condition easily recognizable.' Certainly this patient bears a striking resemblance to their case 1 (H. W. female, aged eighteen years), but the radiographic characters and certain clinical features are entirely different. Apart from an osseous dystrophy this patient does not present any of the other features of the syndrome. The osseous dystrophy also is different. In gargoylism the vertebral bodies in the dorso-lumbar area tend to show a grooved anterior surface and one or more may be tongued, and at this level a kyphos is produced by backward displacement of a body slightly smaller than the others. There is a bilateral coxa valga deformity, an enlargement of the sella, and delay in fusion of the epiphyses, but no unusual density and absence of the epiphyses.

FIG. 5.

(Note difference in ossification of terminal phalanges of toes.)

THE LOWER EXTREMITY. At the age of ten all the bones of the lower extremity showed marked osteoporosis.

Pelvis.—Regular in shape. The three elements were still distinct.

Femora.—At five years the capital epiphysis was ovoid in shape. The neck showed fragmentation and marked displacement as in severe cervical coxa vara. The epiphysis for the great trochanter was present (fig. 6). At thirteen years all the epiphyses and the fragments of the neck had soundly consolidated in a coxa vara position. The lower epiphyses and those of the upper and lower ends of the tibiae and fibulae were present at the age of five years (with the exception of the lower epiphyses of the tibia and fibula) and had fused at the age of thirteen (fig. 7). The diaphyseal extremities were rather irregular in outline and coarse in cancellous texture.

CHONDRO-OSTEO-DYSTROPHY. The original case of this dystrophy, the clinical and radiographic features of which was shown at the Royal Society of Medicine in 1928 (Brailsford, 1929), when the patient was three years of age, presents some features which resemble the present case. It is interesting to know that these two children lived near to one another and played together for several years, but were unrelated. The patient W. T. B. presented radiographic appearances of the spine which resembled an exaggerated form of those seen in gargoylism; he had a prominent kyphosis but he was a bright intelligent good-looking child. Multiple ossific nuclei developed in all his epiphyses, his joints were all swollen. He had no unusual density of his epiphyses and these appeared and fused at normal times. He was kept under periodic radiographic examination until he died aged fifteen in October, 1940. From the age of four years his musculature degenerated. At the age of thirteen years he was 2 ft. 11 in. in height, having gained but 2 in. since he was three years nine months. During the last three years of his life his limbs were flaccid. He was pallid, and periodically he had 'turns' during which he became blue and had profuse sweating from a cold skin. Radiographs in 1939 showed no increase in the length of the limbs or trunk. He then measured 2 ft. 9 in. The long bones were thicker, but the pressure deformities at the ends were more marked. The nuclei for the epiphyses at the knees had fused, but most of the other large epiphyses were fragmented. The vertebrae were compressed and irregular in outline. All the bones showed osteoporosis and none showed normal cancellous structure. The joints were all swollen and the interosseous spaces increased. His appearance, distinct from that shown in my original photographs, was finally that of a most grotesque dwarf.

FIG. 6.

FIG. 7.

Summary

An osseous dystrophy is described, characterized by dense epiphyses which fuse early though development of other ossific centres is markedly delayed. Grotesque dwarfing with apparently normal intelligence is associated with severe spinal curvature and bilateral coxa vara.

Thanks are due to Sister Manaton and Sister Hill of the Royal Cripples Hospital for help with the radiographs.

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OSTEOMYELITIS OF THE SPINE FOLLOWING LUMBAR PUNCTURE

BY

LEONARD FINDLAY, M.D., D.Sc., and F. H. KEMP, M.R.C.P., D.M.R.E.

(From the Radcliffe Infirmary, Oxford)

Case report

The patient was a boy aged one month who was admitted to the Radcliffe Infirmary, Oxford, on March 6, 1942. He was the second child of healthy parents, born on February 2 with a weight of 6 lb. after a normal pregnancy. He was breast fed and progressed satisfactorily till the age of three weeks when he developed a cold in the head and a rash on the face and buttocks. At first the child did not seem seriously upset, for he continued to take his feeds well without any vomiting and to have regular and normal evacuation of the bowel. Two or three days before coming under observation, however, he had been manifestly ill, refusing the breast and seeming breathless; and for twenty-four hours the left eye had been discharging.

On admission to hospital he was noted to be a small, wasted and dehydrated infant weighing 5½ lb. The temperature (rectal) was subnormal —96° F. There was much excoriation of the cheeks, a profuse nasal discharge, purulent conjunctivitis of the left eye and ulceration of the buttocks, scrotum and legs, apparently of a septic nature. Examination of the chest revealed poor air entry and some moist and dry râles generally, but no dullness to percussion. The abdomen was distended with the liver palpable one finger-breadth below the costal margin, but the spleen could not be felt. There were no abnormal neurological signs. The urine presented a deposit of urates, but contained no albumin, blood or pus.

Blood count: Hb. 100 per cent., red blood cells 4,240,000, white blood cells 4,000 per c.mm.

A provisional diagnosis of generalized bronchitis following an upper respiratory infection in a marantic and badly cared for infant was made. Next day, however, slight nuchal rigidity was present, and during a routine examination the child had two short convulsive seizures, each lasting about a minute. This change in the clinical picture raised the question of meningitis and the necessity for an examination of the cerebro-spinal fluid. Lumbar puncture was attempted on two occasions, but no fluid was obtained, and at the time, from the grating of the needle, the operator was conscious that the vertebral column had been injured.

On the following day (March 8) the child seemed better; there had been no recurrence of convulsions, the conjunctival discharge was less profuse, the septic condition of the skin had improved, he was taking his feeds well and had gained some weight; there was, however, slight fever (101·6° F.). Although the child's general condition continued to improve, fever, varying between 101° F. and 103° F., persisted, and on March 11, i.e. four days after the attempted lumbar puncture, the needle track was observed to have become infected, and was discharging pus from which the staphylococcus aureus was grown. On this date the bacteriologist reported that the discharge from the eye revealed the presence of a gram-negative diplococcus indistinguishable from the gonococcus, and in consequence sulphapyridine (M & B 693) was administered by mouth in addition to argyrol 10 per cent., which had been applied locally to the eye since admission. On this date it was also learned that the Wassermann and Kahn tests were negative.

In spite of the administration of sulphapyridine, fever persisted and the local infection at the seat of the lumbar puncture continued to advance. By March 14 a fluctuant swelling requiring incision had developed. Nevertheless, the child's general condition had improved still further, the eye had cleared, the septic state of the skin had almost completely healed, he had continued to take his feeds well and to increase in weight. In view of this general improvement, the apparent localization of the infection to the subcutaneous tissues surrounding the needle track, and especially because the etiological organism was the staphylococcus aureus against which sulphapyridine is not particularly effective, treatment with this drug was interrupted. Thereafter, the local infection rather improved, probably because of the incision of the abscess and the better drainage, and within three days fever had disappeared. However, three days later (March 25) fever returned and examination now revealed swelling of the lumbar region of the spinal column and an x-ray picture showed destruction of the bodies of the second and third lumbar vertebrae and the intervening intervertebral disc space. Treatment with sulphathiazole was now instituted and continued for six days. Within twelve hours of the presentation of this drug the fever subsided, and with the exception of a slight and occasional rise during the following two weeks, the temperature continued within normal limits. In spite of the absence of fever, the local condition of the spine persisted unchanged, and on March 30, oedema of the left leg below the knee made its appearance, and a few days later, the right leg was also noted to be oedematous. The swelling of the left leg extended to the thigh and lower abdomen with considerable glandular enlargement in the groin. Finally, the scrotum was also oedematous. At this stage the left femur felt thickened and x-ray examination revealed periostitis of the shaft, and subluxation of the left hip joint. On April 13 a swelling on the palmar aspect of the second finger of the left hand was observed which x-ray examina-

tion showed to be connected with osteitis of the middle phalanx. This swelling rapidly increased in size, became fluctuant and on incision discharged pus from which staphylococcus aureus was isolated. By this time the swelling of the lumbar spine had further increased and there was present an angular curvature, and on April 21 a skiagram showed great extension of the disease, the bodies of the second and third lumbar vertebrae having almost completely disappeared (fig. 1).

Although the present communication is for the purpose of drawing attention to the risks associated with, and an unusual sequel to, lumbar puncture, it

FIG. 1.—Skiagram showing almost complete disintegration of bodies of 2nd and 3rd lumbar vertebrae with persistence of the spinous processes.

is also of interest to relate that with the institution of treatment with penicillin such a serious and apparently hopeless complication was recovered from. This treatment, begun on April 25, was conducted under the guidance of Professor Florey, who no doubt will incorporate the details of the dosage and the subsequent progress in the general report of his researches with this drug. Hence it may suffice to say briefly that the child, excepting for a further abscess, which developed in the nape of the neck just below the occipital protuberance from which the staphylococcus was also recovered, and which was first noticed two days after the inception of the penicillin treatment, made a good recovery. The various septic foci steadily improved, the sinus at the seat of the lumbar puncture healed, the swelling and deformity of the lumbar region of the spinal column gradually disappeared and the swellings of the finger and at the nape of the neck subsided. Radiological examination showed a return to the normal conditions in the leg and hand and some new bone formation at the situation previously occupied by the bodies of the second and third lumbar vertebrae. The temperature, as previously mentioned, remained at a normal level, the child continued to put on weight and began to laugh and to smile and develop as a normal baby should.

Comment

The course of events in this case would seem to leave no doubt regarding the cause of the calamity. As the result of the attempt at lumbar puncture, a wound of the skin was made in a region not far removed from a definitely septic focus (the buttocks) and it became infected. Although a bacteriological examination of the primary septic condition of the skin was not made, it is not improbable that it was of a staphylococcal nature. Moreover, during the attempt at lumbar puncture, the operator was conscious that one of the vertebrae had been injured, so that a direct track from the skin surface to the vertebral column was produced. The operation wound became septic and the infection travelled along the track of the needle to settle down in the injured vertebral body, with the development of osteomyelitis. Later, there ensued a blood infection with the metastatic foci in the middle phalanx of the second finger of the left hand, in the left femur and left hip joint and in the deep tissues of the neck. It might be considered fortunate that in this case the lumbar puncture was a so-called dry tap, and that the spinal canal was not opened, otherwise a meningitis would have been a further and still more serious complication.

That the vertebral column may be impinged upon by the point of the needle is well known to all familiar with the operation of lumbar puncture, and Pease (1935) has demonstrated, by means of skiagrams with the needle in situ, that both the intervertebral discs and the vertebral bodies may be injured during the operation. Pease found that when the body is flexed, the usual posture during the operation, the needle enters the intervertebral disc, but if the body is not arched, the needle pierces the body of the vertebra. However, in spite of the frequency with which the vertebral column must be injured, especially in the case of the smaller spinal canal of the infant and young child, mishaps ascribable to this factor have seldom been recorded. One would not be surprised if the injured focus in the vertebral column became a nidus for infection, just as is frequently encountered, and indeed is always feared, in connexion with any injury during an infective process. And when it is appreciated that the needle must often pass through an infective focus in the pia arachnoid before reaching the body of the vertebra, the dearth of such sequelae seems all the more remarkable. In a fairly extensive experience of this operation by one of us, this is the first instance of such a nature that he has observed.

The literature, ever since the introduction of this diagnostic procedure, abounds with records of accidents, varying from transient headache and vertigo to sudden death, following lumbar puncture. For the most part, they have been attributed to altera-

tions in the pressure of the cerebro-spinal system consequent on the abstraction of the fluid or to mechanical irritation of the meninges. Occasionally instances of an inflammatory reaction, viz. meningitis (Levy and Cohen, 1925; Reynolds and Wilson, 1934; Symonds, 1925), due more frequently to an endogenous than to an exogenous source of infection (Pray, 1941; Weed et al., 1919), are recorded, but it was not until 1924, some forty-three years after the introduction of the operation, that injury to the vertebral column first finds mention as the cause of any disability following lumbar puncture.

In 1924 Billington recorded thirty-five cases of spondylitis following cerebro-spinal fever. In all, numerous lumbar punctures had been performed. In these cases the chief complaint was of stiffness and pain in the lumbar region which had developed during, or soon after, the attack of meningitis. In sixteen cases the manifestations were purely subjective; in five cases there was present in addition to the pain, definite rigidity of the lumbar spine, and in fourteen cases there was present, as well as the symptoms and physical signs, radiological evidence of disease of the vertebral column. This latter consisted of lipping, spurring and other hypertrophic changes of the third, fourth or fifth vertebrae in all cases; in seven cases there was also thinning or destruction of the disc between the third and fourth or the fourth and fifth lumbar vertebrae, and in one case general spondylitis deformans.

Billington states that he had never observed this clinical picture apart from cerebro-spinal fever and he concluded that the mischief was due to infection by the meningococcus. He recalls that it is not unknown for this organism to cause arthritis and he considered that the infection had been carried to the vertebrae by means of the lumbar puncture needle. As he remarks, 'the spinal puncture may easily afford a direct means of inoculating the lower vertebrae and discs with the meningococcus, and in view of the location of the pathologic conditions in the cases recorded, it appears probable that it is an important etiological factor. The two cases in which there were pathological changes in other regions may represent metastatic infections' (as happened in the present case), 'such as occur in the involvement of joints of the extremities, though apparently less frequently.'

Subsequent observations, however, have cast doubt on Billington's thesis that changes such as were observed by him are necessarily due to infection by the meningococcus, and suggest that they may be caused by some other infective agent, or that they may have a purely mechanical basis.

In 1935 Pease recorded three instances in which an exactly similar pathological picture (pain and rigidity of the lumbar spine with radiological evidence of thinning of an intervertebral disc and sclerosis and lipping of the adjacent vertebral bodies) followed lumbar puncture. Pease's patients were children, but only one was suffering from cerebro-spinal fever. One of the children had infantile paralysis, and in the other child lumbar puncture was performed for the production of an encephalogram.

Pease naturally doubted that the mischief had a bacterial basis. He ascribed the changes to mechanical strain consequent on the puncture of the intervertebral disc with escape of the nucleus pulposus and removal of the normal cushion between the individual vertebral bodies. In support of his argument he stresses the thinning of the discs, which to him is a constant feature, and he recalls the work of Keyes and Compere (1932) who showed experimentally in the dog, (a) that if the disc and neighbouring part of the vertebral body are injured by a scalpel the nucleus pulposus may escape into the spongiosa of the vertebra and produce the condition known as Schmorl's node and (b) that if the disc were incised and the nucleus allowed to escape the disc becomes narrowed and the edges of the adjacent vertebrae become sclerosed and lipped.

It is interesting in this connexion to record that Compere (during a discussion following Pease's communication) said that his experiments referred to by Pease were not comparable with lumbar puncture, as he incised the fibrous capsule of the disc with a scalpel, and he doubted if the nucleus pulposus could escape through such a small wound as that caused by a lumbar puncture needle. At any rate in the dog he could not get results by needle puncture which he obtained by scalpel incision. Compere also said that he was suspicious that in some of the adult cases recorded 'the pathologic changes in the disc may have been the reason for lumbar puncture and not a result of it.' Another important point germane to this discussion was raised at the same time by Barber, who stated that 'Todd and Pyle, in a qualitative study of the vertebral column by direct and roentgenoscopic methods, found the vertebral dimension of the intervertebral discs to vary from 8 to 19 mm. The disc between the second and third lumbar vertebrae averaged 11·3 mm. with a range from 8 to 14 mm.; the disc between the third and fourth lumbar vertebrae averaged 12·4 mm. with a range from 8 to 16·5 mm. and the disc between the fourth and fifth lumbar vertebrae averaged 14·8 mm. with a range from 11 to 19 mm.' Todd and Pyle also found that a lateral roentgenogram gave the measurement of a disc but that an antero-posterior roentgenogram did not.*

In 1936 Milward and Grout reported five instances in which the same clinical syndrome followed lumbar puncture for the induction of spinal anaesthesia. These authors, in view of the nature of their material, also doubted that the changes were the result of an infective process and, like Pease, were inclined to ascribe the lesions to mechanical forces. Whilst they admit that the fons et origo of the lesion in the child may be, as Pease believed, the disappearance of the intervertebral disc, they are doubtful if this is so in the case of the adult. They do not think that a needle puncture is sufficiently large to allow of the escape of the much smaller and better protected nucleus pulposus at this time of life, but are of the opinion that the trauma of the annulus fibrosa by the needle sets up 'an inflammatory reaction with a consequent weakness in the fibrous wall' and in this way permits 'of a gradual escape of the nucleus pulposus.' This view they consider is borne out by the x-ray appearances in three of their cases, 'where

* In a large series of cases of excision of posterior prolapse of the nucleus pulposus for sciatica and followed for long periods after the operation, one of us (F. H. K.) has never observed any radiological change in the adjacant vertebral bodies.

there was only slight erosion of the articular surfaces at the first examination but a complete involvement of the whole joint at a subsequent examination a month or two later.'

The only other communication found dealing with this subject is a case record by Gillman (1940). This refers to a luetic child of fourteen years of age who, after three unsuccessful attempts at lumbar puncture three years previously, complained of severe pain in the back. X-ray examination four days after the operation revealed nothing abnormal, but when repeated one month later because of the persistence of the pain and the appearance of rigidity, narrowing of the space between the third and fourth lumbar vertebrae and relative widening between the second and third and the fourth and fifth was evident. With immobilization of the spine the pain and rigidity ultimately disappeared, but seventeen months after the attempted lumbar puncture, there was discernible on radiological examination erosion of the adjacent articular surfaces of the fourth and fifth and of the second and third vertebrae. This author concludes that the sequence of events is as suggested by Pease.

Whatever be the truth about the etiology of the examples of acute and chronic spondylitis following lumbar puncture previously reported, there can be no doubt that in the present case bacterial infection of the injured spine was the dominating factor.

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PRIMARY CARCINOMA OF THE PANCREAS IN AN INFANT AGED SEVEN MONTHS

BY

BERYL D. CORNER, M.D., M.R.C.P.

Physician to Out-Patients, Bristol Children's Hospital

Primary malignant disease of the pancreas in infancy and childhood is a rarity as indicated by the few cases reported in the literature.

Lymphosarcoma was found in a new-born infant by L'Huillier (1904), and in a girl aged four years by Litten (quoted by Ewing, 1928). Todd (1818) reported a case of a girl aged fourteen years, who having been ill for some months with pyrexia and digestive disturbances, became deeply jaundiced and died. Post mortem, the pancreas appeared scirrhous, and the head of the gland was converted into a solid tumour mass which obstructed the common bile duct, causing gross distension of biliary and hepatic ducts. Rokitansky (1842) and Wedl (1866) both describe a scirrhous condition of the pancreas in new-born infants, but in Wedl's case the mother had syphilis, so that the condition was probably syphilitic and not malignant. Battersby (1844) reports a case of carcinoma in a fourteen-year-old child, and Herringham (1894) in a two-year-old child, but no details of the case are given and in none of these five cases is there any histological confirmation of malignancy.

There are five recorded cases of pancreatic primary carcinoma in childhood in which histological evidence of malignancy has been obtained. Bohn's case (1885) was an infant aged six months who was found to have an abdominal tumour and developed jaundice six weeks before death. Microscopy of the tumour, which was situated in the head of the pancreas, showed that it had a finely meshed alveolar structure in the spaces of which were clusters of medium-sized cubical epithelial cells. There were secondary deposits in the liver and in the glands at the portal fissure.

Kühn (1887) reported a case in a girl aged two years. This child had been ill for about nine months and then developed oedema of her legs and diarrhoea. An enlargement of the liver was found and she died from pneumonia. Post mortem the pancreas was found to be almost completely replaced by a reddish tumour, and there were secondary nodules in the liver. Histology showed that the tumour was a cylindrical celled adeno-carcinoma. Simon's (1889) case was a thirteen-year-old boy, whose symptoms were anorexia and diarrhoea with jaundice eight weeks before death. The whole gland with the exception of a small part of the tail, was involved in a tumour mass, the histology of which was identical with Kühn's case. Bandelier (1896) reports a similar case. Stewart and Stewart (1915) had a case in a nine-year-old boy, in whom pain, anorexia and constipation followed a blow on the abdomen. The child was well-nourished and the only abnormal clinical finding was an irregular mass situated in the left upper abdomen. At operation a tumour of the tail of the pancreas was revealed, the rest of the gland being hard and irregular. A few reddish lymph nodes were seen along the upper border of the pancreas, but there was no other evidence of secondary involvement in the abdomen. Only partial autopsy was performed but microscopically the tumour was found to have a fibrous tissue framework occupied by islets of closely packed cells showing mitotic figures and necrosis. The tumour was named medullary carcinoma of the pancreas.

The following case is reported in view of the early age of the patient, and the scarcity of reports of this condition in childhood in the English literature.

Case report

HISTORY. Betty A. was a full-time baby, born by normal delivery on February 26, 1939. Both parents were healthy, and she had a sister aged two years who was alive and well. She was breast-fed for three months and then weaned on to a cows' milk and water mixture. Her abdomen had seemed large since birth, but at the age of five months the mother complained that it was increasing rapidly in size and seemed very hard. Bowels were usually constipated, appetite was good but the child had always had a good deal of flatulence and magnesia was given regularly. She was admitted to Bristol Children's Hospital on October 19, 1939, because she had been screaming continuously for three days and had vomited once.

EXAMINATION. This revealed an extremely distressed-looking infant, who was well-nourished but very pale. There was no clinical evidence of jaundice or oedema. Weight, 18 lb. 8 oz. Temperature 100·6° F., pulse 160, respiration, 56.

ABDOMEN. This appeared distended with numerous dilated superficial veins. A tumour filled the upper part, extending to the level of the umbilicus on the right, and into the iliac fossa on the left. The lower border of the mass was sharply notched at the level of the umbilicus, and the surface was smooth, except the left lower portion which was definitely nodular. The tumour was typically an enlarged liver. A little free fluid was detected.

FIG. 1.—Betty A. Six days before death. Aged seven months. Note good state of nutrition.

URINE was acid, and contained sugar, but no urobilin or other abnormalities.

INVESTIGATIONS. Wassermann reaction, negative.

Blood count. Haemoglobin 40 per cent., red corpuscles, 3,270,000 per c.mm., average red cell diameter, 7·5μ, white corpuscles, 15,500 per c.mm., polymorphonuclears, 53 per cent., lymphocytes, 38 per cent., monocytes, 9 per cent. Anisocytosis and poikilocytosis marked, and many ring forms. Van den Bergh reaction: direct slight positive, indirect 0·9 unit.

Blood sugar. (Fasting) 113·2 mgm. per cent.

Blood urea. 14·4 mgm. per cent.

Blood cholesterol. 109 mgm. per cent. Blood groups of child and parents O.

PROGRESS. The child remained febrile, temperature varying from 100° to 100·6° F.; she sweated profusely and cried continuously as if in pain. Seven-ounce milk feeds were taken well without vomiting, and there were two relaxed green stools daily.

Eight days after admission, she was given a blood transfusion and laparotomy was performed under general anaesthesia by Mr. Wilfrid Adams. A greatly enlarged liver was found which contained a greyish nodular mass in the left lobe, and numerous other nodules could also be seen. A portion of the nodular mass was excised for biopsy, but owing to the infant's poor condition, the abdomen was closed without further exploration. Death occurred two hours after operation.

BIOPSY REPORT. Poorly differentiated adenocarcinoma. Cells are small with scanty cytoplasm and do not resemble liver cells or bile-duct epithelium.

AUTOPSY REPORT. (Autopsy performed eighteen hours after death by Professor T. F. Hewer.) The body was that of a well nourished female infant with a distended abdomen but no jaundice or other external sign of disease. A recent exploratory laparotomy wound accounted for the presence of a little blood in the abdominal cavity. The liver was greatly enlarged, weighing 1,680 gm. Its width was 22 cm.; its greatest thickness antero-posteriorly was 7 cm. The surface of the liver was regular and rounded on the right side but just to the left of the falciform ligament, the margin turned sharply downwards along a massive lobe of tumour, which accounted for the greater depth of the liver on this side. In the hilum of the liver there were several large lymph glands which were full of necrotic tumour. The gall-bladder and bile ducts were healthy and patent. On section the whole liver was invaded by an irregular yellowish mass of tumour which was necrotic in the centre and contained one area of recent haemorrhage. The liver was not jaundiced. The lymph nodes in the hilum of the liver, alongside the common bile duct and around the head of the pancreas were full of tumour. A large mass of firm tumour was present in the head of the pancreas. Metastases were found in the anterior mediastinal lymph nodes and studded all over the pleural surfaces of both lungs. No tumour was found elsewhere, and the rest of the alimentary tract from mouth to anus appeared healthy.

HISTOLOGICALLY the tumour in the head of the pancreas (fig. 2) consisted of a cylindrical cell adenocarcinoma apparently derived from ducts. It had produced some fibrous tissue reaction. The adjacent pancreatic acini did not appear abnormal and there was no sign of obstruction of pancreatic ducts or of disease in the body or tail of the pancreas. The metastases in lymph nodes, liver and lung were less well differentiated and had not produced a scirrhous reaction. The liver tissue alongside the tumour was not cirrhotic and there was no bile duct dilatation. Many branches of the portal vein were full of tumour.

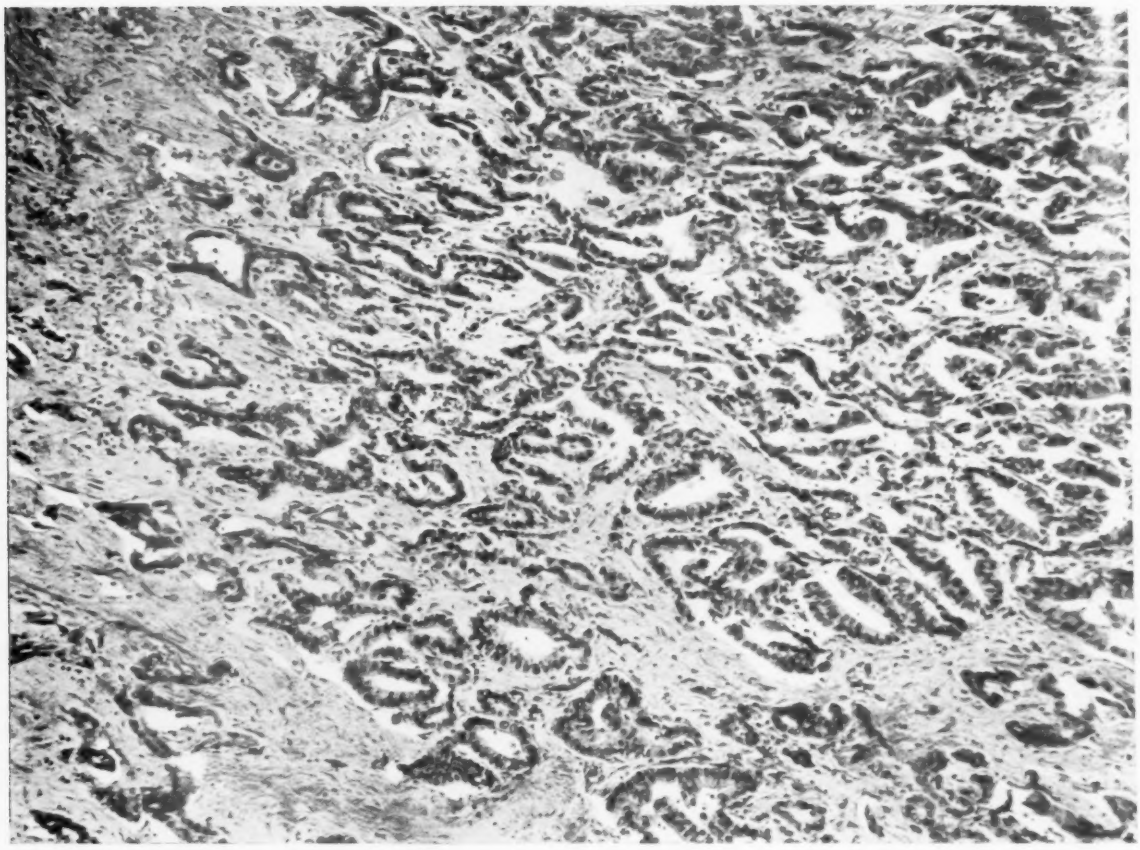

FIG. 2.—Photomicrograph of section through tumour in head of pancreas.

Discussion

The commonest clinical features found in cases of pancreatic carcinoma are cachexia, anorexia and other digestive disturbances, jaundice and a palpable abdominal tumour. In this case the outstanding clinical signs were the abdominal tumour and severe anaemia; the absence of any wasting (see fig. 1) and good appetite were notable. Glycosuria, which was present in this case, was found in forty-three out of two hundred and one cases at all ages collected from various authors by Kiefer (1927); it was not noted in any of the other cases referred to in children. The duration of the disease in the other childhood cases has been described as several months, most of the cases only being under observation for the last few weeks; in this case the history would indicate that there was definite hepatic enlargement at the age of five months, and therefore the primary growth probably arose shortly after birth. Bohn's case (1885) is the only other case of definitely established pancreatic carcinoma that has been reported in an infant under two years old.

The differential diagnosis lay between carcinoma of the pancreas and carcinoma of the intra-hepatic bile ducts. The former diagnosis may be accepted since the tumour in the pancreas was better differentiated than that in the liver, and closely resembled a moderately scirrhous carcinoma derived from the pancreatic ducts, whilst there was no indication of the biliary obstruction in the liver that is usually associated with malignant cholangioma. Evidence of spread of the tumour within the branches of the portal vein also favours a pancreatic origin.

Thanks are due to Professor Hewer for the autopsy report on this case, and for the photographs.

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COARCTATION OF THE AORTA WITH CEREBRAL ANEURYSM

BY

J. N. O'REILLY, D.M., M.R.C.P.

Medical Superintendent of St. Margaret's Emergency Hospital, Epping

AND

O. W. CHAPMAN, M.B., Medical Registrar to the Hospital

Coarctation of the aorta is a rare condition. Death is due to rupture of cerebral aneurysm in so small a percentage that the following case seems worth reporting:

A boy, C. L., aged thirteen years, was admitted to hospital on March 3, 1941, with the history that four days previously while playing he had had a sudden general constricting sensation in the head. He had gone home and there vomited. The constricting sensation localized to a severe frontal headache which had continued. There had been periodical vomiting and the bowels were constipated. Prior to admission he had been given an enema during which he had collapsed, and his doctor had reported that he had had a fit. On admission the boy was semi-conscious, the pupils were equal and regular and reacted to light and accommodation. The cranial nerves were intact. There was considerable neck rigidity and Kernig's test was positive. The left knee jerk was present but the right knee jerk and both ankle jerks were absent. The biceps jerks were present and normal. The supinator jerks were exaggerated. The left plantar reflex was flexor but the right was doubtful. Examination of the fundi showed papilloedema. Sensation, movement and power in the limbs appeared normal. The cardio-vascular system showed some enlargement of the heart with the apex beat just outside the nipple line. The rhythm was regular. There was a rough systolic murmur in the precordium, best heard in the third left interspace. Blood pressure 230/140 mm. Hg. No other marked physical signs.

Lumbar puncture showed increased pressure of the cerebrospinal fluid, about 28 cm. of water, and marked blood-staining homogeneously distributed through the fluid. Examination showed 75,000 red blood cells per c.mm., 60 white blood cells per c.mm., protein 0·09 per cent., no other abnormality, and culture sterile.

During the forty-eight hours after admission the patient's condition improved, he became quite conscious and mentally normal, and on March 6 the headache was slight, blood pressure 180/120 mm. Hg and lumbar puncture showed the fluid straw coloured, still under increased pressure and sterile. The only additional clinical sign was that the right pupil was considerably larger than the left.

On March 9 the patient's headache was again severe and he was noticeably less alert. Plantar responses were extensor. Lumbar puncture showed deeply blood-stained fluid under 18 cm. pressure. Temperature was up to 101° F. This condition continued during the next three days. By March 12 the headache was less and the cerebrospinal fluid was yellow and showed no evidence of fresh bleeding.

Full examination at this time revealed that the femoral arteries could not be palpated. The blood pressure in the popliteal artery was 105/100 mm. Hg (the diastolic figure is somewhat doubtful). On these findings a diagnosis of coarctation of the aorta was made. An x-ray examination of the heart was made about this time and showed absence of the aortic knuckle which confirmed the diagnosis. The boy's general condition remained fairly satisfactory with temperature swinging up to about 100° F. until March 20. On this day he complained of headache and he vomited. Later he became unconscious and lumbar puncture showed heavily blood-stained fluid. The next day he was still unconscious, the fluid was still deeply blood-stained and the temperature rose to 107° F. Tepid sponging brought it down to 103° F., but it rapidly returned to 107° F. and within a few hours the patient died.

Post-mortem. On removing the sternum the heart was seen to be somewhat enlarged, and there was considerable dilatation of the aorta above the insertion of the ligamentum arteriosum. Below this the thoracic aorta quickly resumed its normal size and relations. On opening the heart the aortic valve was found to have two cusps only, one of apparently normal size and the other much enlarged and having a median raphe. The ascending and transverse aorta appeared normal on opening apart from the dilatation, but on passing a probe a complete obstruction was found at the insertion of the ligamentum arteriosum (fig. 1). The ligamentum itself was patent on the pulmonary side for about half its length and then became a solid cord. The left subclavian artery and the left thyroid axis were dilated. There was gross enlargement of the internal mammary arteries which could be followed down quite easily to their anastomoses with the deep epigastric vessels. The descending aorta tapered rapidly and the iliac vessels were small. On opening the cranium a large mass of blood clot was found lying at the base of the brain and tracking down into the spinal canal. This was found to be coming from a ruptured aneurysm of the anterior communicating artery at its junction with the left anterior cerebral artery (fig. 2). The blood had torn up the brain substance to some extent in both frontal lobes and it had ruptured into the anterior horn of the left

FIG. 1.—Heart and aorta showing constriction at insertion of ligamentum arteriosum.

lateral ventricle (fig. 3). There was another small aneurysm on the left choroidal artery. No other abnormalities were found.

Discussion

Coarctation of the aorta is a well-known but by no means common abnormality.

Abbott (1928), quoting Paul White's figures, gives the frequency as two in five thousand consecutive autopsies. Blackford (1928) reports it as occurring once in 1588 consecutive autopsies. Other authors give similar figures. Turning to the clinical cases described, Blackford enumerates seventy-eight cases which he found in the literature, but of these only four were in children. Between 1928 and 1938 Eisenberg (1938) found about forty cases had been described in adults between seventeen and sixty-six

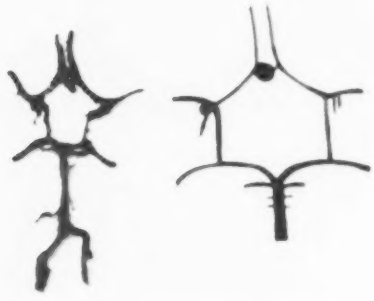

FIG. 2.—Circle of Willis, showing aneurysms: diagram alongside.

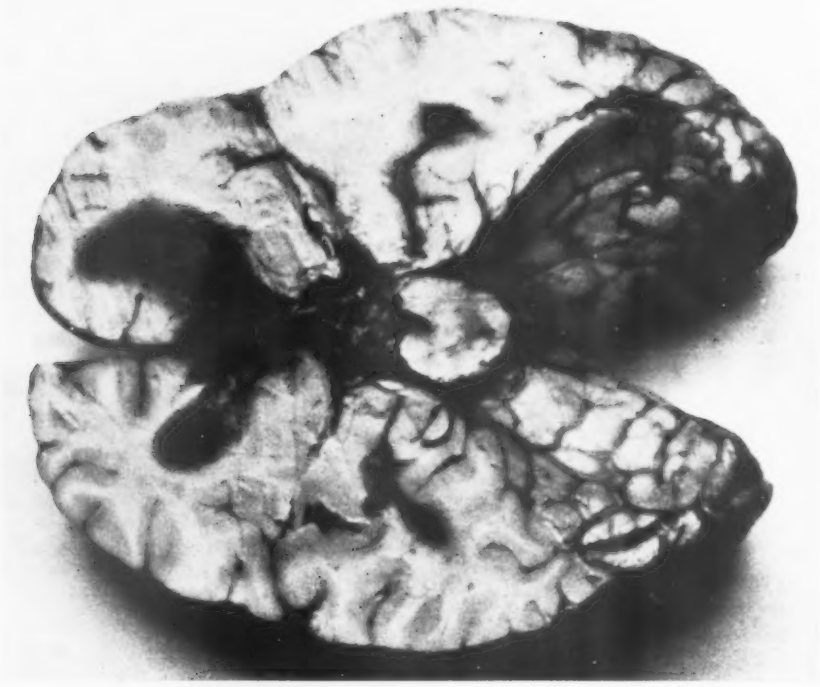

FIG. 3.—Section of brain, showing bloodclot in the lateral ventricle.

years, whereas only eleven cases are recorded as occurring in children. To the latter he adds three of his own, two discovered in the course of routine examination and one which attended his cardiac clinic complaining of pain in the chest and legs on walking. He calls attention to the comparative rarity with which coarctation is diagnosed in children and says that palpation of the femoral pulses should form part of the routine examination of every child.

The diagnostic point is the contrast between the forceful bounding pulse and the high blood pressure in the arms with the feeble or absent pulse and lower pressure in the legs. A systolic murmur is also usually audible along the left border of the sternum. Evidence of collateral circulation around the scapula may be absent or unconvincing in children. Radiologically there is absence of the aortic knob in the postero-anterior view and a defect in the aortic arch in the left oblique view (Fray, 1930). Fray also describes the notching of the ribs seen in the x-ray film, an appearance first described at autopsy by Meckel.

The location of the stenosis is at the insertion of the ductus arteriosus in fifty per cent. of cases (Abbott), and just above or just below in the remaining fifty per cent. The ductus is commonly closed, either ligamentous throughout or in a few cases open on the pulmonary side (Fletcher, 1842).

The degree of stenosis is variable. Out of two hundred cases Abbott found it complete in forty-seven. Associated abnormalities of considerable degree are not common, with one exception, that of bicuspid aortic valve which appears in about twenty-five per cent. of the cases. This condition is a true ante-natal abnormality due to fusion of the two cusps, and it is not uncommon to find, as in the present case, a median raphe either completely dividing the cusp into two, or itself fenestrated and only partially dividing the composite cusp.

The mode of death is usually decompensation or by rupture of the aorta. Mycotic aneurysm due to bacterial endocarditis is also frequent. A certain number of deaths are due to cerebral haemorrhage. In Abbott's series thirteen cases had 'spontaneous' rupture and five deaths were due to ruptured cerebral aneurysm. It is possible that in some of the other thirteen cases death was in fact due to rupture of an aneurysm.

Cerebral aneurysm is not a common condition, but it is one which has been described by a number of authors.

Eppinger first suggested it as a cause of cerebral haemorrhage in healthy young adults as long ago as 1887. Since then it has been described on a number of occasions, notably by Gowers (1893), Symonds (1923) and Parker (1926). Parker groups the aneurysms anatomically, giving the middle cerebral artery as the commonest site, 29 per cent. of a series of 154 cases. He quotes Gowers for the figure of eight aneurysms of the anterior communicating artery out of the same series (5·3 per cent.).

The principal symptoms of aneurysm in the anterior portion of the cranium are severe neuralgic pain over the forehead and hyperaesthesia with loss of the corneal reflex. There may be paralysis of the third, fourth and sixth cranial nerves and exophthalmos. Sometimes there is a central scotoma with pallor of the optic disc on the side of the aneurysm and mild signs of pyramidal disturbances on the opposite side. If the aneurysm leaks there is increase of the focal signs, confusion or stupor, the temperature is raised up to about 101° F.; the cerebrospinal fluid is blood-stained and under pressure. Parker describes a case of leak and finally rupture of a cerebral aneurysm in a healthy young man who was found also to have coarctation. The lesion was at the junction of the posterior communicating artery and the middle cerebral, and another aneurysm was found at the junction of the anterior communicating with the anterior cerebral artery. More recently Walker and Livingstone (1938) have described a case of coarctation which died following rupture of an aneurysm of the left vertebral artery within the cranium. The cause of aneurysm is attributed by Green (1928) and Forbus (1930) to a herniation of the intima of an artery at its junction with another artery. They have both shown that the muscular coat is deficient at this point and hernia is brought about by the constant high pressure due to the coarctation.

Summary

A case of recurrent cerebral haemorrhage occurring in a boy of thirteen years is described. The case was diagnosed as being due to leakage from a cerebral aneurysm associated with coarctation of the aorta, and this was confirmed at post-mortem.

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CAROTINAEMIA IN A SUCKLING

BY

M. L. THOMSON, M.D., M.R.C.P.

Assistant Physician, Royal Manchester Children's Hospital

The following instance of carotinaemia in a suckling seems of sufficient interest to merit a brief clinical memorandum.

The mother, aged twenty-five, was referred on account of 'jaundice' unaccompanied by any symptoms of ill health. Her last child was born six months previously and weighed 8 lb. at birth. The baby was breast fed until two months old, when the mother consulted her practitioner because of the onset of 'jaundice' both in herself and her child. She was advised to stop breast feeding and the baby's 'jaundice' gradually disappeared. The mother's 'jaundice,' however, persisted. On examination of the mother there was sallow yellow pigmentation of the whole body with the exception of the sclera which were clear. Clinical examination was otherwise negative. Investigation showed that the icteric index was 8, though the serum bilirubin was only 0·1 mgm. per cent. By the three-layer test, in which equal parts of serum, alcohol and petroleum ether are shaken and allowed to separate, it was shown that the pigment was extracted by the upper layer of petroleum ether. It was evident, therefore, that the pigmentation was due to carotinaemia. Enquiry into her diet elicited that for the past eleven months she had been eating two to three carrots of some 4 in. in length daily in addition to a normal consumption of cabbage and cooked carrots. Her weekly consumption of raw carrots averaged two to three pounds. At the time of the examination she was still eating these quantities.

Examination of the baby showed a plump, well-nourished healthy infant with a slight sallow tint overlying the normal pinkness of the skin. The three-layer test on the baby's serum was negative, the serum bilirubin being 0·2 mgm. per cent. and the icteric index 2. The mother said that prior to stopping breast feeding the baby's skin had become quite yellow.

The transmission to a suckling of excess of carotene by the mother's milk is an odd outcome of maternal dietetic excess.